Host-microbial crosstalk along the gut-liver axis in metabolic disease

Background: Extensive alterations in microbiome composition and function have been described in response to Western dietary patterns and in particular in obese individuals (1). Increased abundance of opportunistic pathogens is hypothesized to be a key driver of inflammation associated with these conditions and active contributions of the microbiota to the progression of metabolic diseases such as non-alcoholic fatty liver disease (NAFLD) have been reported(2, 3). However, the specific pathways of crosstalk between mucosal immunity, intestinal physiology and the microbiota in metabolic disease remain poorly understood. The Harb group has expertise in the study of interactions between metabolism and immunity in the lung and the liver and has established a range of metabolic disease models (obesity, non-alcoholic fatty liver disease [NAFLD], non-alcoholic steatohepatitis [NASH]) **(4-8)**. The Slack group has extensive expertise in the mechanistic study of host-microbial interactions and has established worldwide unique facilities to carry out real-time volatile metabolomics under full-barrier axenic conditions **(9-13).**

Aims: We aim in this project to investigate how metabolically induced alterations in intestinal physiology affect microbiota composition and function and how they contribute to hepatic and systemic metabolic inflammation. Additionally, we aim to assess the mechanisms driving host-microbial interactions that lead to metabolic disease progression and thus identify potential therapeutic targets.

Approach: We will perform a systematic mapping of host-microbial interactions along the gut-liver axis using gnotobiotic mice, including mice carrying patient-derived microbiota. Disturbances in intestinal motility, barrier function, and intestinal, hepatic and systemic immunity will be assessed in these models and dependence on microbiome will be characterized. We will use mice carrying murine endogenous microbiota as well as mice carrying human patient-derived microbiota established through fecal microbiome transfer from lean and obese individuals as well as NAFLD patients. These studies will identify mechanistic links between the microbiome, altered intestinal homeostasis and metabolic inflammation and shall identify microbial regulators of metabolic dysfunction and inflammation. Within-host population dynamics and genome-scale metabolic models of microbiota species established in the Slack group can further generate mechanistic insight into disease-associated microbiota shifts, and vaccine-based interventions to alter the abundance and behaviour of individual microbiome components. Together this allows host and microbiota metabolism to be tracked over the circadian rhythm in gnotobiotic models, simultaneously with quantification of the growth and behaviour to intestinal microbes. Rational interventions to increase or decrease intestinal motility, barrier function, inflammatory state and/or pH will be used to understand the mechanistic drivers of biomarker shifts in the volatile metabolome and/or microbiome composition. Mechanistically resolved biomarker panels can then be translated into more complex animal models and patients. Working iteratively between the two groups will allow us to develop rational interventions that ameliorate dysbiosis and prevent opportunistic infections in metabolic disease states.

Topics for the PhD studentships will be:

- **Ad i)** Study metabolically induced alterations in intestinal physiology, motility, and immunity, and their contribution to hepatic and systemic metabolic inflammation (Dresden)
- **Ad ii)** Delineate the role of altered metabolic landscape and altered intestinal physiology in driving alterations in microbiota composition and microbiota function in metabolic disease (Zurich)
- **Ad iii)** Identify underlying mechanisms driving host and microbial biomarkers of metabolic disease progression and identify potential therapeutic targets (Dresden & Zurich)

Work to be performed in Dresden: Students will identify individual pathways of host-microbial interactions contributing to the pathogenesis of metabolic inflammation. This includes generating humanized microbiota mouse models of NASH and detailed analysis of pathophysiology and mammalian pathways involved.

Work to be performed in Zurich: Students will elucidate the underlying mechanisms which drive an expansion of proinflammatory host-microbial interactions in metabolic diseases. This

will include rational physiological interventions in gnotobiotic mouse models with real-time metabolomics and microbial within-host population dynamics quantification, as well as computational modelling to disentangle the metabolic versus physiological contributions of disease to dysbiosis.

Added value through the collaboration between Dresden & Zurich: The Harb lab provides expertise in mouse models of metabolic diseases and the study of host-microbial interactions in the regulation of intestinal and hepatic immunity. The Slack laboratory has extensive expertise in gnotobiotic studies including a unique setup for comprehensive metabolomic assessment under axenic conditions, within-host population dynamics of microbes, microbiome engineering technologies and computational modelling. Expertise of the two PIs will be combined to identify novel therapeutic and diagnostic targets in metabolic inflammation.

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