ABSTRACT

This thesis explores the relationship between diet, gut microbiota, and metabolic health, with a particular focus on their association with non-communicable metabolic diseases (NCDs) such as obesity and type 2 diabetes (T2D).

The aim of the first study is to assess compositional and metabolic differences in gut microbiota between healthy lean long-term vegans and omnivores. The study reveals that while the gut microbiota composition is not significantly different between the two groups, there are significant differences in the fecal, serum and urinary metabolome. These differences may be attributed to the different availability of substrates in the diet, as the vegan diet is associated with a shift from a proteolytic to a saccharolytic fermentation program. Our results support the hypothesis of both resilience and metabolic flexibility of the adult gut microbiota.

In addition to taxonomic analyses, this dissertation also includes metabolomics to evaluate the functional manifestations of the gut microbiota. We introduce a novel method to assess the ability of the gut microbiota to produce beneficial metabolites with a specific focus on butyrate synthesis using qPCR quantification of bacterial butyryl-CoA:acetate CoA-transferase. *In silico*, we identified bacteria among the human gut microbiota that possess the *but* gene, designed and validated six sets of degenerate primers covering all selected bacteria and developed a method to normalize gene abundance in human fecal DNA. We validated this method in subjects with opposite dietary habits and metabolic phenotypes - lean vegans (VG) and healthy obese omnivores (OB) - with known fecal microbiota and metabolome composition.

Furthermore, the effects of inulin treatment on glucose homeostasis in pre/diabetic patients were investigated. A three-month intervention with inulin under clinical trial conditions was associated with an overall improvement in glycemic indices, although the response was highly variable, with a shift in microbial composition towards a more favorable profile and an increase in serum butyric and propionic acid concentrations. Using multi-omics analysis, we identified biomarkers that predict treatment success. If further validated, these predictors could improve the estimation of outcomes of inulin interventions and contribute to personalized dietary management in early-stage diabetes.

Finally, the fourth study investigates the therapeutic potential of fecal microbial transfer (FMT) using vegan microbiota to treat non-infectious diseases. It uses a humanized mouse model to examine the effect of a Western-type diet (WD) and inulin supplementation on obesity, hepatic steatosis, and glucose metabolism. We found that vegan microbiota alone did not protect against the adverse effects of WD and inulin supplementation reversed steatosis and normalized glucose metabolism. This phenomenon was related to a change in microbiota composition and an increase in saccharolytic fermentation at the expense of proteolytic fermentation. Our results highlighted that the success of fecal microbiota transfer in the treatment of metabolic noninfectious diseases depends not only on the microbiota transfer itself but also on subsequent dietary interventions involving inulin or other fiber and/or dietary changes.

This dissertation provides some new insights into the relationship between diet and the gut microbiome, particularly in relation to the therapeutic potential of targeted manipulation of the gut microbiota in the treatment of obesity and T2D. The study highlights the importance of dietary interventions, such as inulin or fiber supplementation, and emphasizes personalized dietary approaches to modify gut microbiota and improve metabolic health.

Key words:

Gut microbiome, metabolome, metabolic diseases, vegan diet, western type diet, animal models, type 2 diabetes, OMICS data