Environment-host-microbe interactions shape human metabolism

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Appendices

Summary

A variety of microbial communities exist throughout the human body. Advances in technologies (sequencing & bioinformatics), coupled with the establishment of human perspective cohorts such as the Human Microbiome Project (HMP, 2012), Dutch LifeLines-DEEP study (LLD, 2016), Belgian Flemish Gut Flora Project (FGFP, 2016) and others, have now enabled the characterization of the remarkable inter-individual variations in the gut microbial composition. These variations can be further linked to variable human phenotypes, including cardiometabolic disease, inflammatory bowel disease, diabetes and others, highlighting the importance of the gut microbiome - a rising star that widely associates with various complex diseases as reported by the analyses from human cohort-based studies - that may affect susceptibility to complex diseases via its interaction with genetics and the environment **(chapter 1)**. However, the mechanistic explanation underlying how the gut microbiome, and its interactions with genetics and environment, influences host health and disease remain largely unexplored.

As a first step toward filling this knowledge gap, **(chapter 2)** links the taxonomical and functional composition of the gut microbiome to plasma lipidomics that reflect the risk of cardiovascular disease (CVD). Here we found that the gut microbiome can explain up to 11.1% and 16.4% of the variation in plasma lipidomics in our population-based and obesity cohorts, respectively. We also identified obesity-specific microbial associations for lipid compositions in the VLDL, IDL and LDL lipoprotein subclasses. These results provide primary evidence that the gut microbiome may potentially influence CVD by regulating lipid metabolism.

To further dig into the biological mechanisms that underlie microbiome-lipid interactions, **chapter 3** focuses on bile acids, a category of steroids that is implicated in the etiology of CVD-related conditions such as dislipidemia. The metabolism of bile acids involves both genetic and microbial activities. While numerous novel microbial and genetic associations to plasma and fecal bile acids had been identified previously, our in-depth analysis on the functional potential of microbes pinpointed microbial species such as *Ruminococcus sp_5_1_39BFAA*, which not only closely relates to plasma lipids and liver fat content but also has bile acid deconjugation capacity that is reflected in the genetically encoded functionality of its genome. These detailed associations supply us with a putative *in silico* mechanistic interpretation for how the gut microbiome can influence human lipids metabolism by regulating bile acids.

To move beyond microbiome-lipid interactions towards developing systematic understanding about environment-genetics-microbiome interactions in human metabolic health, **Chapter 4** concentrates on the broad plasma metabolome measurements generated by un-targeted metabolomics techniques. Here, we found thousands of novel metabolite

associations to diet, genetics and the gut microbiome and showed that diet and microbiome dominate over genetics in contributing to the inter-individual metabolome variations. Mendelian Randomization (MR) and mediation analyses further suggested *in silico* causal relationships in diet-genetics-microbiome interactions and putative mechanisms underlying complex diseases. For instance, we saw a novel beneficial effect of the gut species *Eubacterium rectale* in decreasing the plasma levels of toxic p-cresol and p-cresol sulfate, two metabolites related to cardiometabolic risk and chronic kidney disease.

As the above chapters are based on cross-sectional studies, they could not capture whether microbial changes over time, and their interactions with metabolic changes, are relevant to changes in human health status. **Chapter 5** takes advantage of the longitudinal design of the LLD cohort to provide *in silico* causalities between the gut microbiome and human metabolic health. In this chapter, we also move beyond the gut microbiome composition by charactering the genetic stability and instability of the gut microbes. We found that the genetic makeup of many the gut microbes show long-term stability and an individual specificity that can fingerprint of the host with up to 95% accuracy. In contrast, temporal changes in unstable microbiomes demonstrate the potential of developing novel therapy by modifying gut microbiome composition.

Although differential abundances of microbes in health and disease have been well characterized, and their interactions with multiple biological layers have begun to be explored, the diverse microbial communities in our gut make up a complicated ecosystem in which microbes can exchange or compete for nutrients, signaling molecules or immune-evasion mechanisms through ecological interactions that are far from fully understood. **Chapter 6** deciphers microbial interactions in order to detect key microbes in health and disease. We find that the strengths of 38.6% of species co-abundances and 64.3% of pathway co-abundances vary significantly between health and disease cohorts. In addition, hundreds of microbial co-abundance relationships showed IBD- and obese-specific effects that could replicated in independent cohorts. Moreover, we identified key microbes that potentially dominate the diseased gut microbial ecosystem, e.g. *Escherichia coli, Oxalobacter formigenes* and *Actinomyces graevenitzii* in IBD. Our study shows that microbial dysbiosis in disease may not only be driven by differences in microbial abundance level but also by shifts in microbial interactions that are mirrored in co-abundance analyses, which extends our current knowledge about the role of the microbiome in disease. In particular, the disease-specific microbial interactions we identified provide further insights into functional dysbiosis in IBD and obesity.

Finally, in **Chapter 7**, I highlight our major achievements and discuss

their limitations and remaining challenges, underlining the importance of decoding microbial metabolic functionalities and the integration of multi-functional omics together with cutting-edge artificial lab technologies in order to get better mechanistic understanding about the role of gut microbes and its interaction with genetics and environment factors in human health and disease.

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Curriculum vitae

Lianmin Chen was born on November 23rd, 1991 in Jiangsu, China. In 2010, he started his bachelor research in Animal Nutrition and Cell Biology at Yangzhou University, China, under the supervision of Prof. Mengzhi Wang. He graduated *Cum Laude* in 2014. After graduation, he started his master's research in Microbiology at Yangzhou University, China, under the supervision of Prof. Hongrong Wang and was awarded the National Scholarship for Postgraduates in 2016. In 2017, he obtained his master degree (*Cum Laude*) and was awarded a joint fellowship from the China Scholarship Council (CSC) and University of Groningen (RUG) to support his PhD research at the Departments of Pediatrics and Genetics, University Medical Centre Groningen (UMCG), University of Groningen, the Netherlands, under the supervision of Prof. Jingyuan Fu, Prof. Folkert Kuipers and Prof. Alexandra Zhernakova. During his PhD, he applied bioinformatic approaches to study the impact of environment-genetics-microbiome interactions on human cardiometabolic health.

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