

Tim Hensen

In silico Modelling links Microbiome-derived Metabolites to Risk Factors for Alzheimer's disease

Introduction

The gut microbiome is increasingly recognised for its role in Alzheimer's disease (AD). Recent studies have proposed an involvement of the gut microbiome in AD pathogenesis by influencing human metabolism via metabolic cross-talk with the host. However, mechanistic pathways connecting the gut microbiome to AD pathogenesis remain unknown. Recent developments in the fields of gut metagenomics and metabolic modelling have made it possible to generate microbiome personalised whole-body metabolic models (WBMs). WBMs can be algorithmically interrogated to describe metabolic phenotypes of the host-gut system, by calculating metabolite production capacities. Due to the deterministic nature of WBMs, these metabolite production capacities can be linked to individual microbes in the WBMs, resulting in mechanistic hypotheses of host-microbiome cross-talk. For this study, we generated WBMs from a large cross-sectional cohort with the aim to employ them for obtaining mechanistic hypotheses on the link between gut microbiome alterations and risk of developing AD.

Methods

Gut metagenomics was obtained from a cross-sectional cohort of 1,065 healthy ageing individuals from the Rotterdam study to personalise 1,065 WBMs. Metabolite production capacities were predicted in the WBM blood compartments for 63 AD-related metabolites using flux balance analysis. We then correlated the predicted fluxes with major risk factors of AD, including age, the AD risk gene APOE, global cognition, and sex. These correlations were further contextualised with measured serum metabolomics from the same individuals. Finally, microbial drivers of the flux predictions were identified in the gut microbiomes.

Results

Our metabolic modelling based analysis found increased production capacities of L-arginine in older individuals, which was driven by *Parabacteriodes distansoni* and *Bilophila wadsworthia*. The APOE E4 genotype was associated with increased deoxycholate fluxes, a correlation that was replicated for *Eggerthella lenta*, the main producer of deoxycholate in the WBMs. Furthermore, lower global cognition correlated with increased production capacities of several microbe-derived bile acids including, lithocholate, 7-dehydrocholate, 7-dehydrochenodeoxycholate, and deoxycholate. In the serum metabolomics, host-produced precursors of these microbe-derived bile acids were found to also negatively correlate with global cognition. Finally, male-specific correlations were found with lower global cognition for flux predictions of creatine, L-arginine, S-adenosyl-L-methionine, L-tryptophan, and isobutyrate, highlighting the potential role of sex in host-gut interplay and cognitive health.

Discussion

Taken together, our findings suggest a potential sex-specific involvement of the gut microbiome in AD pathogenesis. Moreover, we hypothesise preclinical shifts in bile acid producing bacteria, such as *Eggerthella lenta*, to be linked to an increased risk of developing AD. If confirmed, antibiotic targeting of these gut microbes could provide a potential means of delaying the onset of AD.