Diet-induced modifications to human microbiome reshape colonic homeostasis in irritable bowel syndrome

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Introduction

Changes in microbiome composition are associated with a wide array of human diseases, turning the human microbiota into an attractive target for therapeutic intervention. Yet, clinical translation of these findings requires the establishment of causative connections between specific microbial taxa and their functional impact on host tissues. Here, we infuse gut organ cultures with longitudinal microbiota samples collected from therapy-naive patients with irritable bowel syndrome (IBS) under a low-fermentable oligo-, di-, mono-saccharides and polyols (FODMAP) diet. We show that post-diet microbiota regulates intestinal expression of inflammatory and neuro-muscular gene sets. Specifically, we identify Bifidobacterium adolescentis as a diet-sensitive pathobiont that alters tight junction integrity and disrupts gut barrier functions. Collectively, we present a pathway discovery platform for mechanistic dissection and identification of functional diet-host-microbiota modules. Our data support the hypothesis that the gut microbiota mediates the beneficial effects of a low-FODMAP diet and reinforce the potential feasibility of microbiome-based therapies in IBS.

Research Layout

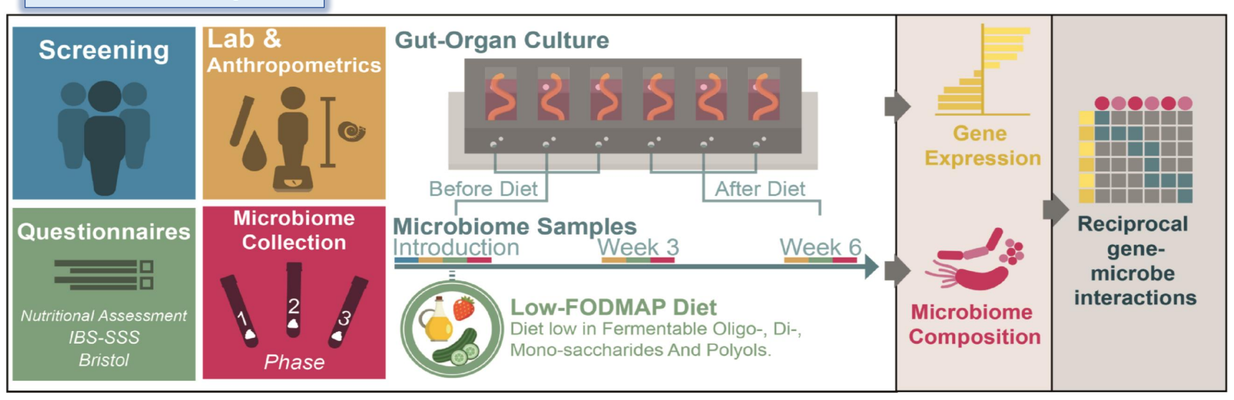

Figure 1: Experimental design: a longitudinal cohort of therapy-naive patients with IBS-D (n = 10; patients exhibited IBS symptoms for at least a year) included clinical evaluations and microbiome sampling throughout 6 weeks of low-FODMAP diet. Microbiome composition was determined by 16S rRNA gene sequencing. The functional impact of post-diet microbiota was determined by ex vivo stimulation of colon organ cultures with patient microbiota samples pre- and post-diet. Colonic gene expression was determined using bulk RNA sequencing followed by predictions of reciprocal associations between specific microbial taxa and differentially expressed host genes.

Post-diet microbiota modifies colonic gene expression ex vivo

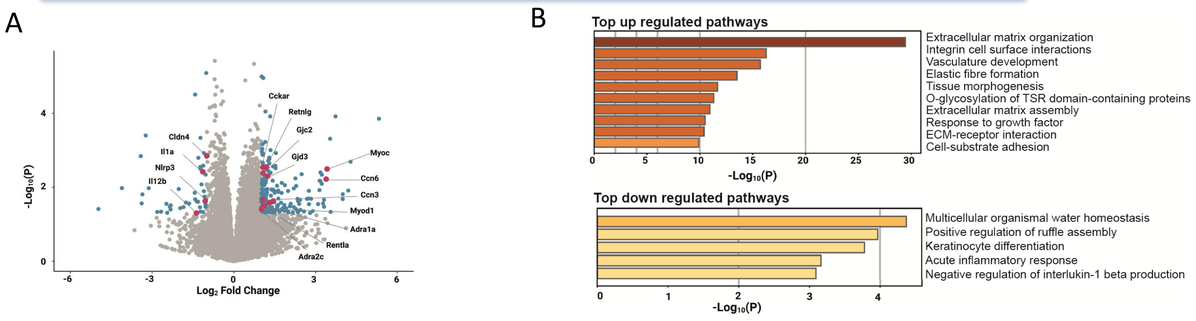

Figure 2: **(A)** Volcano plot indicating changes in gene expression comparing colon organ cultures infused for 2 h with post-diet (6 weeks) versus pre-diet microbiota (n = 3 for each time point, in duplicates, in total 12 samples sequenced). Transcripts significantly up- or downregulated (blue; fold change >2, p < 0.05), as well as selected genes of interest (red), are highlighted. **(B)** Gene Ontology analysis of differentially expressed genes using Metascape.

Introduction of *B. adolescentis*, but not *B. fragilis*, impaired epithelial barrier integrity

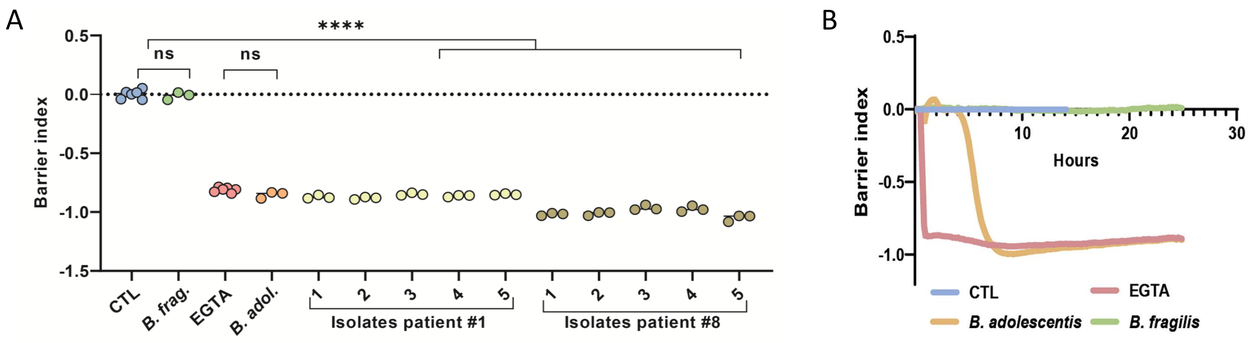

Figure 3: Dynamic measurements of *trans*-epithelial electrical resistance (TEER) for CaCo2 monolayers using Maestro Edge MEA system (Axion BioSystems). **(A)** 10 isolations of *B. adolescentis* colonies from pre-diet fecal samples collected in our clinical cohort (2 patients with IBS-D, 5 isolates per patient; bacterial classification was validated by Sanger sequencing of the 16S gene of isolated clones) Normalized TEER values after 24 h. **(B)** Dynamic measurements of *trans*-epithelial electrical resistance versus time.

B. adolescentis disrupts TJ integrity and epithelial barrier functions

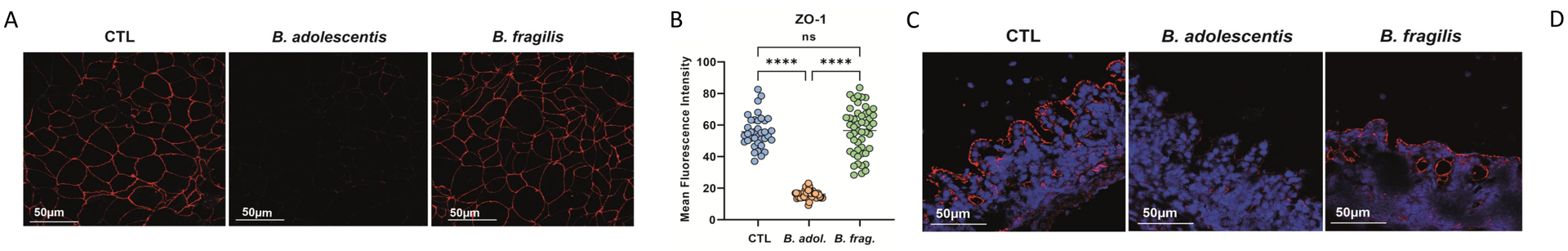

Figure 3: **(A, B)** Confocal microscopy images stained for ZO-1 **(A)** and quantification of mean fluorescence intensity (MFI) **(B)** of CaCo-2 cells following different treatments. **(C, D)** Confocal microscopy images of ZO-1 (red; DAPI nuclear stain in blue) **(C)** and quantification of MFI **(D)** in colon organ cultures at 4 h post-stimulation with *B. adolescentis* (*B. adol*), *B. fragilis* (*B. frag*), or sterile medium (CTL) using the gut organ culture system. Data acquired by three independent experiments.

B. adolescentis disrupts TJ integrity and increases gut permeability in vivo

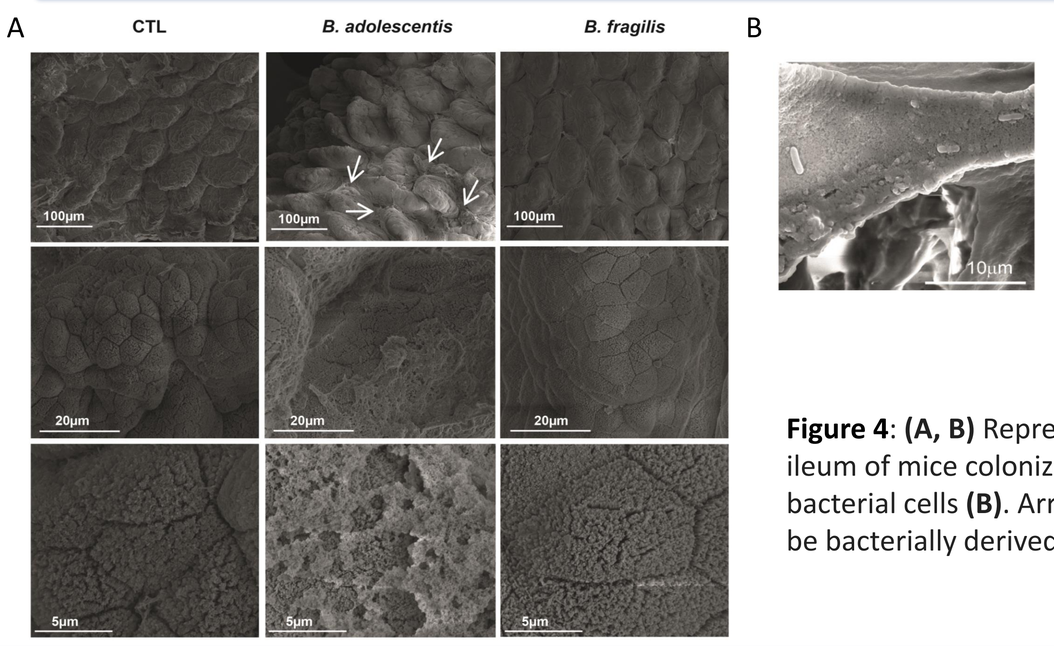

Figure 4: **(A, B)** Representative SEM images of the terminal ileum of mice colonized as indicated **(A)** and EPS-associated bacterial cells **(B)**. Arrows indicate sites of matrix suspected to be bacterially derived exopolysaccharide.

Conclusions

- Low-FODMAP diet alters microbiome composition in patients with irritable bowel syndrome
- Post-diet microbiota rapidly modifies intestinal gene expression
- *B. adolescentis* alters tight junction integrity and disrupts gut barrier functions
- The gut organ culture system uncovers functional diet-host-microbiota