P071 MODULATION OF THE MUCUS LAYER BY BIFIDOBACTERIUM DENTIUM PROVIDES PROTECTION IN A MODEL OF COLITIS
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Background: The intestinal mucus layer serves as a critical interface between the environment and the host. Patients with inflammatory bowel disease (IBD), particularly ulcerative colitis, exhibit reduced synthesis and secretion of the mucus protein MUC2 and decreased mucus thickness. This in turn promotes immune activation and inflammation. The clinical relevance of the mucus layer is emphasized by the need to address strategies to modulate this barrier. Although bifidobacteria represent only 3–6% of the healthy adult fecal microbiota, their presence has been associated with numerous health benefits, including bolstering mucus production. However, the molecular mechanisms that underlie these positive effects appear to be strain-specific and are not well defined. We hypothesized that the human-derived Bifidobacterium dentium would increase intestinal mucus synthesis and expulsion via specific metabolites. We also speculated that modulation of goblet cells would be beneficial during colitis.

Methods & Results: In silico genome analysis revealed that B. dentium lacked the enzymatic repertoire required for degradation of mucin glycans. Consistent with these findings, we found that B. dentium could not use mucin glycans as a primary carbon source in vitro. To examine mucus modulation in vivo, germ-free mice were mono-associated with live or heat-killed B. dentium. Live B. dentium mono-associated mice exhibited increased colonic expression of goblet cell markers (Kruppel-like Factor 4 (KLF4), Relmβ, trefoil factor 3 (TFF3), Muc2, and several mucin glycosyltransferases compared to both heat-killed B. dentium and germ-free counterparts. Likewise, live B. dentium mono-associated colon had increased acidic mucin-filled goblet cell numbers denoted by MUC2 and PAS-AB staining. In vivo, B. dentium secreted products, including acetate, were able to increase MUC2 levels in T84 cells, mouse colonoids and human colonoids. We also identified that B. dentium secreted products, such as GABA, stimulated autophagy-mediated calcium signaling and MUC2 release. To identify whether B. dentium could enhance MUC2 production in mice harboring a complete microbiota, specific pathogen-free (SPF) germ-free mice were treated with live B. dentium by oral gavage. Administration of B. dentium increased the inner mucus layer compared to controls. Moreover, in a TNBS model of colitis, B. dentium treated mice had increased goblet cell numbers and increased MUC2 mRNA. Mirroring these findings, B. dentium treated mice lost less weight, had improved histology and had decreased levels of TNF, KC (IL-8), and IL-6. MUC2 mRNA. Mirroring these findings, B. dentium treated mice lost less weight, had improved histology and had decreased levels of TNF, KC (IL-8), and IL-6.

Conclusions: This work illustrates that B. dentium enhances the intestinal mucus layer and goblet cell function via upregulation of gene expression and autophagy signaling pathways with a net increase in mucin production. Ultimately, these pathways may be targeted for the development of novel therapeutics.

P075 SER-287, AN INVESTIGATIONAL MICROBIOTHEPHERAPY, INDUCES WIDESPREAD METABOLOBIC AND HOST TRANSCRIPTIONAL CHANGES RELATED TO CLINICAL REMISSION IN PATIENTS WITH ACTIVE MILD-TO-MODERATE ULCERATIVE COLITIS
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Background: Firmicute bacteria and the metabolites they produce are perturbed in ulcerative colitis (UC) patients. SER-287, an oral formulation of live Firmicutes spores, was found to be safe and effective in achieving clinical remission in a Phase 1b clinical trial in mild-to-moderate UC. We assessed changes in the stool metabolome and host transcriptome among remitters and non-remitters as a measure of SER-287’s pharmacodynamics.

Methods: 58 UC subjects (modified Mayo score 4–10) were randomly assigned to one of four 8-week induction treatment arms preceded by a 6-day antibiotic pre-conditioning phase as follows: a) placebo/placebo b) placebo/SER-287 weekly c) vancomycin/SER-287 weekly or d) vancomycin/SER-287 daily. Clinical remission was defined as a Total Modified Mayo Score ≤2 plus an endoscopic subscore ≤1. Stool samples were evaluated for microbiome composition (whole metagenomic sequencing), targeted and global metabolomics (liquid chromatography-mass spectrometry) and transcriptomics (RNA-Seq with mucosal biopsy) at baseline and at week 8.

Results: Vancomycin/SER-287 daily was associated with higher rates of clinical remission compared to placebo/SER-287 weekly, vancomycin/SER-287 weekly or placebo/placebo (40%, 13.3% 17.6% and 0%, respectively; p<0.024 for the comparison of daily SER-287 versus placebo/placebo). Significant changes in microbial-associated metabolites (bile acids, indole, taurine, and arachidonate) were associated with clinical outcome across all arms (p<0.05, Mann-Whitney; Figure A). Similar associations with treatment were also observed (p<0.05, Mann-Whitney). Host transcriptomic changes associated with clinical outcome across arms included decreased expression of genes associated with signaling of TNF, NF-kappaB and IL-17, as well as increased expression of genes associated with the metabolism of the short chain fatty acid propanoate (adjusted p-value<0.05, gene set enrichment analysis, GSEA; Figure B). Similar associations with treatment were also observed (adjusted p-value<0.05, GSEA).

Conclusions: In this Phase 1b study of SER-287 the highest rates of remission were associated with daily dosing of SER-287, preceded by vancomycin pre-conditioning. Across treatment arms, clinical remission was associated with a wide range of metabolomic and transcriptomic changes relevant to UC pathogenesis. Changes in metabolomics and transcriptomics are associated with immune cell recruitment and activation, epithelial integrity and mucosal barrier function, giving insights into the mechanism of action of this microbiome therapeutic.

Metabolite abundances in clinical remitters and non-remitters at baseline and Week 8 for select metabolites. Metabolites shown have p-value<0.05 (Mann-Whitney U) comparing remitters and non-remitters at Week 8. Points outside of the box-and-whiskers indicate outliers.

KEGG pathways found to be significantly differentially expressed between clinical remitters and non-remitters. Directionality of expression is given in the third column. All p-values are calculated using gene-set enrichment analysis (GSEA) and adjusted for multiple testing.

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