Identifying Patterns Of Metabolic Dysfunction In The Pathogenesis Of Inflammatory Bowel Disease

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Introduction: Over three million Americans suffer from inflammatory bowel disease (IBD), a lifelong condition of the digestive tract characterized by inflammation, persistent diarrhea, and abdominal pain. Given that the etiology of the condition is currently unknown, there are no treatments that specifically target the pathologies of IBD, and existing broad treatment options such as surgery and immunotherapy are very costly. A prominent hypothesis on the pathogenesis of IBD involves the impact of the commensal gut microbiota and its metabolites on the dysregulation of host metabolism and immunity within the intestinal epithelium. Deficiencies in the mitochondria of intestinal cells impact the severity of IBD. Compositional modifications to the gut microbiota, which are induced through antibiotic treatments, or probiotic combinations that promote the colonization of "healthy" bacteria within the gut, have been found to improve symptoms of IBD. However, the lack of insight into specific microbiome compositions and their impacts on the metabolic networks within the gut hinder the development of a therapy. Using a published dataset containing biopsy transcriptomics data from control and ulcerative colitis (UC) patients, this project aims to investigate the complexity of unique host-microbiota interactions through the design and validation of computational metabolic models that are specific to the patient.
Materials and Methods: We aim to design metabolic models that are patient-specific to address the unique composition of each individual's microbiome and the metabolic state of their intestinal epithelium. To do this, we constrained a global model of patient metabolism using biopsy transcriptomics data from both control and UC patients. Analysis of RNA-Seq data was done with Kallisto, DESeq2, and vegan, which were used to quantify and normalize transcripts for each patient. These transcripts were then aggregated to the gene-level. Lastly, the GIMME algorithm was used to incorporate patient gene expression data, a genome-scale metabolic network reconstruction, and a set of cell-specific target metabolic functions to produce patient-specific metabolic reaction flux models for epithelial cells. Metabolic reaction fluxes were predicted for each patient using flux balance analysis and linear programming, and analyzed with a random forest classifier to determine correlations between the metabolic reaction networks and the expression of IBD pathologies.
Results and Discussion: Several gene families involved in the inflammation response, including SERPIN and Serum amyloid A, are upregulated in IBD patients. PERMANOVA analysis shows multivariate significance for the downregulation of many mitochondrial gene families, including complexes IV and V, in IBD patients. These complexes are responsible for the final two steps in oxidative phosphorylation, and differences in their expression across control and IBD patients lend support for targeted analysis focused on metabolism. Comparing metabolic fluxes across all patient-specific models shows that oxidative phosphorylation proceeds at a lower rate of metabolite turnover in IBD patients, supporting the case for metabolic dysfunction in IBD. Principal component analysis performed on patient fluxes reveals three distinct groups not strictly characterized by diagnosis or disease severity, suggesting three distinct phenotypes beyond the disease state. Future work will involve analysis of paired microbiome composition data to determine if these three phenotypes are influenced by the microbiome.

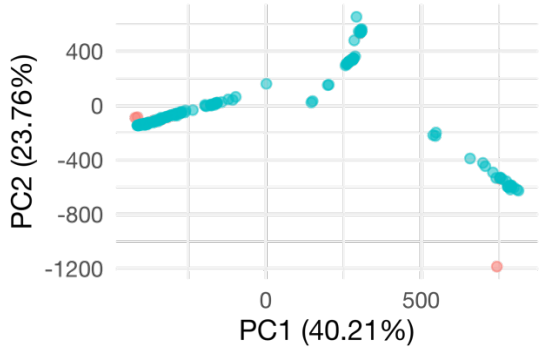

Figure 1. Principal component analysis plot showing variances in metabolic flux across control and IBD patients. Control patients are labeled red and IBD patients are labeled blue.

Conclusion: The analysis of patient-specific metabolic models reveals significant differences in immune and metabolic functions between control and IBD patients. These models can help provide insights on microbiota-induced metabolic dysfunction in IBD that may be caused by a lack of vital metabolites produced by certain bacterial species, with the ultimate goal of developing an IBD-targeted probiotic or antibiotic. Finally, these results can serve as a baseline for future studies that investigate possible mechanisms of pathogenesis in IBD.