Short-Chain Fatty Acid Production: Predictive Functional and Genomic Analysis of the Microbiota in Crohn's Disease for Novel Plasmid-Based Therapy

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Because of the strong association between microbial imbalance, decreased short-chain fatty acid (SCFA) production, and Crohn’s disease (CD) onset, microbiota-targeting therapies are crucial for remission, yet many prove ineffective. This study aims to evaluate fecal microbiota transplantation (FMT), a newly introduced treatment, based on taxonomic and functional changes concerning microbial SCFA synthesis in CD patients. Most importantly, this project provides a novel model for CD treatment via plasmid-based promotion of SCFA production. First, patient sequences (untreated CD, transplantation-treated CD, healthy; n=42/group) were downloaded from the Sequence Read Archive. The QIIME 2 and PICRUSt2 programs were used to analyze the abundances of taxonomic features and metabolic pathways within the samples. To establish mid-biotic target bacteria, the sequences of untreated CD patient taxa and select SCFA-synthesizers were compared in BLAST. Favorable plasmids were chosen based on Mahalanobis distance calculations. Ultimately, FMT significantly increased the abundances of SCFA-producing taxa and enzymes (phosphate butyryltransferase, methylmalonyl-CoA carboxyltransferase, phosphotransacetylase, acetate kinase) involved in SCFA synthesis ($p<0.05$). Several taxa (n=13) were deemed target hosts, with all percent identities greater than 80% ($E<0.001$). Mahalanobis distances for multiple plasmid-bacteria pairs were less than 10 ($P>0.50$), indicating high similarity. The corresponding plasmids (n=8) were selected as the optimal vectors. Overall, the mid-biotics therapeutic model has the potential to induce permanent remission and allow for CD patients to reap myriad benefits (such as those temporarily derived from FMT) without having to undergo surgery or other invasive procedures.

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Fourth Award of $500