Antibiotic-Induced Alterations in Gut Microbiota and Their Effect on Mucus Production in the Cystic Fibrosis Colon

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Introduction: Cystic fibrosis (CF) is a genetic disorder caused by mutations in CFTR, leading to thick mucus accumulation in the lungs and frequent respiratory infections requiring antibiotic treatment. We hypothesized that antibiotics could have off-target effects on the gut microbiome and intestinal architecture in CF patients. **Methods:** We conducted 16S sequencing and non-targeted metabolomics via LC-MS/MS on fecal samples from pediatric CF patients and healthy children. Samples were collected from children without antibiotic exposure for 30 days and CF patients currently on antibiotic regimens. We measured the mucin proteins MUC1 and MUC2 in intestinal biopsy specimens through immunostaining and assessed MUC2 levels in mucus-producing cells after antibiotic exposure via qPCR and immunostaining. To evaluate bacterial community functions, we cultivated bioreactors from stool samples of both groups and treated them with various antibiotics, applying sterile supernatants to mucus-producing cells to examine MUC2 levels. **Results:** 16S RNA sequencing revealed that CF children had significantly altered gut microbiota compared to non-CF children. Stool samples from CF children on antibiotics showed decreased Firmicutes (e.g., Anaerostipes, Ruminococcus, Blautia) and Acintobacteria (e.g., Bifidobacterium), while Bacteroidetes (e.g., Bacteroides, Parabacteroides) were elevated. Non-targeted metabolomics indicated a significant reduction in amino acids and metabolites promoting colonic mucus due to antibiotic use. Immunostaining of colonic biopsies showed decreased mucus-filled goblet cells, lower MUC2 levels, and reduced sialic acid in CF patients on antibiotics compared to non-CF individuals and CF patients without recent antibiotic exposure. This mucus depletion was particularly notable with certain antibiotic classes. In vitro, antibiotics did not affect mucus expression or protein in mucus-producing cells, but metabolites from untreated bioreactors upregulated MUC2 production, while those from antibiotic-treated bioreactors did not. **Conclusions:** Our findings indicate that antibiotics significantly alter gut microbiota and deplete metabolites essential for mucus production. This underscores the importance of considering antibiotic type in CF management, as certain therapies may worsen gastrointestinal complications by disrupting microbiota balance and reducing critical mucus-promoting metabolites.