deletion of calcineurin and NFAT, IEC-specific deletion of B7-H3 and B7-H4 or antibody-mediated blockade of B7-H3 unleashed cytotoxic CD8+ T cell responses and protected from intestinal tumor development in mice, suggesting a central role of myeloid calcineurin in the regulation of T cell responses to intestinal tumors. Together, these studies describe a novel pathway of calcineurin-dependent cross-talk between epithelial, myeloid, and lymphoid cells, which promotes tumor development through inhibition of cytotoxic T cell responses.

**NEUTROPHILS RESTRICT TUMOR-ASSOCIATED MICROBIOTA TO DAMPEN COLON TUMOR GROWTH AND INVASION**

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**Background and Aims:** Neutrophils are among the most prevalent immune cells in the microenvironment of colon tumors and are largely believed to favor colon tumor growth and are predictive biomarkers for colon cancer patients. Clinical trials targeting neutrophil trafficking in cancer are initiated. However, very little is known about neutrophil function in the initiation of colon tumorigenesis. Methods: Colitis-associated colon cancer was induced in mice with conditional deletion of neutrophils (Ly6G<sup>−/−</sup>Mcl1<sup>wt/wt</sup>) and wild-type littermates (Ly6G<sup>−/−</sup>Mcl1<sup>fl/fl</sup>). Sporadic colon tumorigenesis was assessed in neutrophil deficient and neutrophil replete mice with conditional deletion of colon epithelial Apo (Gr2<sup>−/−</sup>CreERT<sup>−</sup>Apo<sup>−/−</sup>). Primary colon tumor tissues from these mice were assessed by histology, RNA-sequencing, quantitative polymerase-chain reaction, and fluorescence in situ hybridization analysis. Fecal and tumor-associated microbiota were assessed by 16S rRNA sequencing. Results: In inflammation-induced and spontaneous colon tumor models, depletion of neutrophils increased growth, proliferation, and invasion of colon tumors. Mechanistically, RNA-sequencing analysis identified several anti-microbial and inflammatory genes were dysregulated in neutrophil-deficient colon tumors. Neutrophil depletion correlated with increased tumor-associated bacteria, increased proliferation, heightened DNA damage, and heightened inflammatory response through IL-17. 16S rRNA sequencing identified microbiota composition changes between neutrophil deficient and wild-type colon tumors. Remarkably, antibiotics treatment and IL-17 inhibition in neutrophil deficient animals dramatically reversed tumor growth, proliferation, and invasion. Mechanistically, bacteria through IL-17 regulated influx of intra-tumoral B-cells which were important for increased tumor growth and progression. Conclusions: Our findings indicate a critical role for neutrophils in the repression of colon tumor growth and progression through restriction of tumor-associated inflammatory responses and bacteria.

**FECAL MICROBIOTA TRANSPLANTATION FOR THE TREATMENT OF OBESITY: A RANDOMIZED, PLACEBO-CONTROLLED PILOT TRIAL**

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**Introduction:** Humanized mouse models suggest the gut microbiome may be a causative factor in obesity and may be mediated by the gut hormone glucagon-like peptide 1 (GLP-1), an anorectic peptide. Fecal microbiota transplantation (FMT) from lean donors have shown promise in metabolic syndrome; however, the role of FMT from a lean donor in obese patients has not been explored. METHODS: 125 metabolically healthy lean donors (BMI 18.5-23 kg/m<sup>2</sup>) were enrolled in a randomized (1:1) placebo-controlled trial of weekly FMT vs placebo capsules for 6 weeks treatment period, or identical placebo capsules. A single healthy lean donor (BMI=17) was used. Patients were assessed with a mixed meal tolerance test at baseline, week 6 and week 12 post-FMT, at which biomarkers GLP-1 and leptin were measured. Stool was collected at baseline and 1, 4, 6, 8, and 12 weeks post-FMT. The primary outcomes were safety and change in the AUC for GLP-1 at 12 weeks compared to baseline. Secondary endpoints include gut microbiome profiles and diversity as well as bile acid profiles and diversity as well as bile acid profiles at 12 weeks post FMT. Additional endpoints include a decrease in BMI and waist circumference at week 12. Standard stool microbiome (16S rRNA) and bile acid (liquid chromatography-mass spectrometry) analysis was performed. RESULTS: We enrolled 22 patients, 11 in each arm. There were no significant differences between the FMT and placebo arms (baseline BMI 40.8± 4.8 vs 41.1± 5.0, p=0.75, age 44±3 years vs 43.3± 12.8, p=0.84, male 1 vs 1, p=1.0). There were no serious adverse events in either arm. Overall, there was no increase in the AUC of GLP-1 in either group at week 12 compared to baseline. The change in leptin AUC between week 12 compared to baseline revealed an increase in the placebo group only (48± 390 vs 309, p<0.001). At week 12, no early changes in BMI were noted in either group (0.3±1.2 vs 0.6± 1.2, p=0.51). We observed global signals of donor community engraftment following FMT, including an increase in alpha diversity (Fig 1A) and increased similarity to stool samples from the FMT donor (Fig 1B); these trends were not observed in the placebo arm. Of the 200 operational taxonomic units we identified as engrafting from the donor, many were enriched in a separate normal BMI healthy cohort (n=60) and decreased at baseline in the obese study patients (Fig 1C). Engraftment was sustained in the treatment group through the duration of the study. Bile acid analysis suggest a sustained decrease in taurocholic acid in the FMT arm, comparable with the donor, not seen in placebo (Fig 2). CONCLUSION: FMT from a healthy lean donor in obese patients was safe and led to engraftment of donor-specific taxa, however, dose-finding studies and longer follow up are required.