1325 BARIATRIC SURGERY-INDUCED MODULATION OF GUT MICROBIOTA IMPROVES RESPONSE TO αPD-1 IMMUNOTHERAPY IN PRECLINICAL MODEL OF BREAST CANCER AFTER BARIATRIC SURGERY

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Background History of bariatric surgery is associated with reduced risk and improved outcomes of subsequent breast cancer, including lower stage at diagnosis, fewer metastases, and higher immunotherapy response rates in patients.[1 2] One potential mechanism of bariatric surgery-induced protection is modulation of the gut microbiome and associated circulating microbially derived metabolites. Importantly, bariatric surgery reduces obesity-associated dysbiosis of the gut microbiota in both patients and preclinical models,[3–5] which we hypothesize primes the microbially derived metabolite profile to activate anti-tumor immunity and reduce tumor burden.

Methods Pooled cecal contents were obtained from donor C57BL/6J female mice who were either obese on high fat diet or formerly obese following surgical weight loss. Recipient C57BL/6J female mice had their commensal microbiome ablated via broad spectrum antibiotic cocktail prior to fecal microbial transplant (FMT). Cecal samples were introduced via oral gavage prior to and following E0771 breast cancer cell injection to ensure sustained transplantation of the donor microbes. αPD-1 immunotherapy or IgG2a isotype control was administered intraperitoneally every other day from the time tumors became palpable until study endpoint. Tumor progression was monitored for 21 days. At endpoint, flow cytometry was conducted on tumors and spleens. Plasma and bile samples were collected for GC-MS profiling of microbially derived metabolites. Tumors and cecal contents were saved for 16S microbiome sequencing, which was analyzed by a DADA2 pipeline.

Results Weight loss due to bariatric surgery prior to tumor engraftment protected against obesity-associated tumor burden and improved immunotherapy response. Microbiome analysis of cecal contents shows increases in Phylum *Firmicutes*, which is associated with elevated metabolite production. FMT samples from surgical weight loss donors resulted in increased efficacy of αPD-1 immunotherapy in recipient mice, both slowing tumor progression and significantly reducing tumor burden at endpoint. Microbiome sequencing confirms successful transplant of microbes. FMT of microbes from weight loss donors resulted in elevated infiltration of CD8+ T cell subsets into the tumor microenvironment, including tissue resident memory cells. Further, microbes decreased circulating secondary bile acids and increased circulating primary bile acids. One secondary bile acid, lithocholic acid (LCA), correlated positively with increased tumor burden and is a candidate driver of immunosuppression. LCA was significantly reduced with αPD-1 treatment in mice receiving weight loss microbes.

Conclusions Herein, we show that reduced tumor burden and improved response to immunotherapy after bariatric surgery is transferrable. We demonstrate that gut microbiota are sufficient to contribute to improved response to αPD-1 immunotherapy in breast cancer after bariatric surgery.

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Ethics Approval Mouse studies were performed in accordance with UTHSC IACUC protocol #21.0224.0

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