Background Immunotherapy has revolutionized patient treatment across cancer types; however, the majority of patients still do not respond, and the reasons for this are unclear. The gut microbiota has been linked to immunotherapy response in melanoma, but the contributing factors to a ‘pro’ or ‘anti’ tumor microbiome remain unknown. Dietary factors, most notably, fiber intake, have been shown to support anti-tumor immunity, while diets high in fat or sugars are associated with poor response. Interestingly, artificial sweeteners (sucralose, saccharin), previously considered to be inert, were recently shown to dysregulate the gut microbiome. Therefore, we hypothesized that microbiome shifts due to artificial sweetener consumption may limit anti-tumor immunity and immunotherapy response in cancer.

Methods Using a mouse model of anti-PD1 responsive cancer (MC38), we sought to determine the impact of sucralose consumption on immunotherapy efficacy. We administered sucralose in the drinking water of mice during tumorigenesis and anti-PD1 treatment and assessed tumor burden, survival, and immune infiltration via spectral immunofluorescence. Lymphocytes were isolated from the tumor and surrounding tissues on day 15 for 5’ single cell RNAseq and flow cytometry to assess TCR clonality and T cell function. We assessed potential direct impacts of sucralose on T cells and tumor cells through in vitro cell killing and functional assays. In addition, we characterized shifts to the gut microbiome and metabolites through 16S rRNAseq and metabolomics from the stool during tumor progression and anti-PD1 treatment.

Results Sucralose, but not sucrose, supplementation in the drinking water ablated response to anti-PD1 in the MC38 mouse model (40–60% CR in controls, 10–20% CR in sucralose). Interestingly, this phenotype could be recapitulated through select antibiotic treatment or fecal microbe transfer (FMT) from sucralose treated animals. Sucralose reduced T cell functionality [cytokine production, proliferation, and cell killing] and increased T cell exhaustion [inhibitory receptor expression, loss of mitochondria] within the tissue. Most notably, we have found that sucralose consumption correlates with lack of response to immunotherapy in melanoma patients treated with anti-PD1.

Conclusions Here, we demonstrate for the first time that supplementation of artificial sweeteners leads to drastic shifts in the gut microbiome and a significant reduction in anti-PD1 response in both mouse and man. The gut microbiome is both necessary and sufficient for this loss of response, indicating that artificial sweeteners may represent a barrier to effective immunotherapy. Overall, these findings suggest that select dietary intervention or FMT may be required to boost response to current checkpoint inhibitors.

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