Impact of a Whole Foods Based High Fiber Diet on Gut Microbiome in Melanoma Survivors

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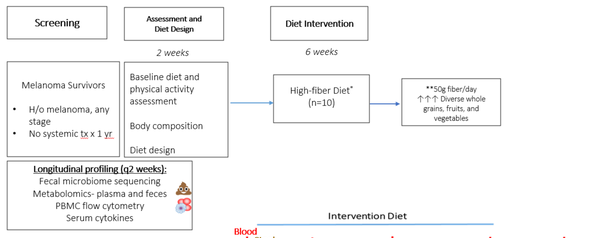
Introduction

- The development and approval of checkpoint inhibitor immunotherapy (ICI) has revolutionized the treatment of many cancers. However, patient responses are mixed.
- Recent evidence has demonstrated that the gut microbiome influences response to ICI(1).
- Observational data in melanoma supports that a habitual high-fiber diet is associated with a pro-response microbiome and improved response to ICI; further, in mouse models, fiber manipulation can impact response to ICI(2).
- Additionally, fiber consumption can shape microbiome metabolic output (3) and, in turn, host metabolism (4).
- Towards testing our hypothesis that a whole foods, plant-based, fiber-rich diet can favorably modulate the microbiome, we first conducted a pilot feasibility study of a high-fiber dietary intervention (HFDI) in melanoma survivors and conducted exploratory profiling of the gut microbiome.



Methods

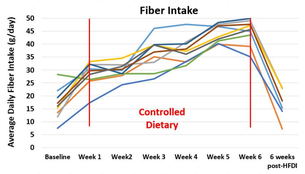
- Study design: Ten melanoma survivors were enrolled to a 6-week high-fiber diet intervention (HFDI) study. As a controlled feeding study, participants were provided with all meals from our Bionutrition Research Core for the duration of the six-week study. The provided diet was isocaloric to energy needs and targeted 50 grams of fiber daily, derived from whole fruits, vegetables, legumes, and whole grains.
- Diet records were obtained at baseline to assess usual diet, throughout HFDI to measure compliance, and then at 6 weeks after the intervention was complete.
- Sample collection: Blood and stool were collected every 2 weeks for exploratory microbiome and immune profiling.
- Whole genome shotgun (WGS) sequencing: DNA was extracted, and library was prepared using 250 mg of fecal sample from the participants. These libraries were sequenced by CosmosID. The data were processed with MetaPhlAn3. (https://huttenhower.sph.harvard.edu/metaphlan/) (5) and alpha-diversity, beta-diversity, and taxonomic abundances processed with ATIMA (https://github.com/cmmr/atima).
- Statistical analysis: Analysis is only shown for 5 of the 9 patients as blood and stool analysis of the 4 other patients is not yet completed. Alpha diversity (Inverse Simpson) were compared across different timepoints. Beta diversity among individuals was ordinated using Principal Coordinate Analysis (PCoA). Linear mixed effects model with random intercept was used to assess the longitudinal trend of the taxa or pathway abundance. Square-root transformation was employed. Due to the exploratory nature of this study, adjustment of multiple comparisons was not conducted. P values presented in this poster are unadjusted p values calculated based on screening (SCRN) vs week 6 (W6).
- Pathway analysis: pathways analyzed in this study were chosen based on whether they involved short chain fatty acid (SCFA) production or some other specific carbohydrate-processing pathway (6). Carbohydrate-processing pathways were divided into 10 subcategories: Amino Acid Degradation, Anaerobic Respiration, Pentose Phosphate, Glyoxylate Cycle, Fermentation, Sugar Degradation, Sugar Biosynthesis, Coenzyme A Biosynthesis, TCA Cycle, and Glycolysis. Only Histidine, Glutamate, and Lysine degradation were included in Amino Acid Degradation because of SCFA products.
- Relative abundance in Figure 5 was calculated by dividing the sum of the absolute abundance of all pathways related to a specific subcategory of carbohydrate-processing pathways by the sum of the absolute abundance of all carbohydrate-processing pathways in the microbiome metabolome.
- Fold change in abundance from baseline for each genus was calculated by comparing abundance at each timepoint with that at screening for each patient. Mean and standard error at each time point were assessed.

HFDI was Tolerable with Excellent Compliance

A

Participant	Age (yr)	Sex (M/F)	BMI (Kg/m²)	Stage of Melanoma	Prior systemic treatment (completion date)	Fasting Glucose (mg/dL)	Baseline Record Fiber Consumption (grams) Week Avg.
2	48	F	29.8	Uveal	N/A	114	22.00
4	25	F	33.6	IIIB	Pembro (12/2016)	97	13.43
3	53	M	27.6	IIIB	Ipi (5/2017)	108	11.86
6	63	F	40.0	Uveal	N/A	129	15.29
7	28	F	24.2	IA	N/A	108	7.43
8	49	F	20.1	IA	N/A	N/A	28.3
9	46	M	35.7	IA	N/A	119	19.29
10	74	M	39.7	IIIC	Nivo (12/2019)	100	17.14
11	43	M	27.8	IA	N/A	104	16
Overall	49	60% F	30.1	N/A	N/A	108	15.05

B



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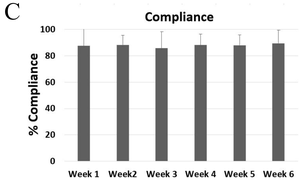

Figure 1: A. Participant baseline characteristics. B. Average daily fiber intake per participant. C. Average weekly compliance with consuming provided diet.

Baseline microbiome composition demonstrates expected heterogeneity across participants

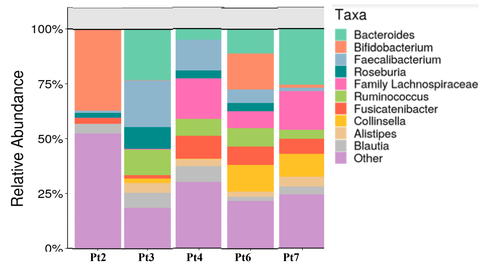

Figure 2: baseline microbiome taxonomic composition for each patient.

Microbiome Alpha and Beta Diversity throughout HFDI

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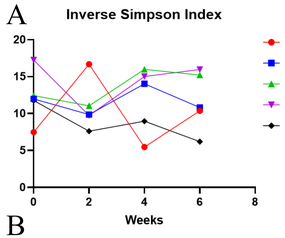

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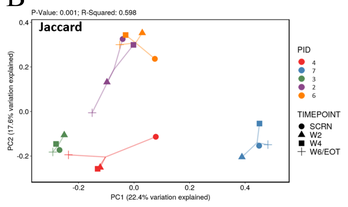


Figure 3: A: Alpha diversity over time in each patient. No consistent trends were observed. B: Beta diversity by principal over time for each patient. Each patient has their own baseline beta diversity, but changes from that baseline were not consistent among all patients.

Relative Abundance of Selected Taxa Through HFDI

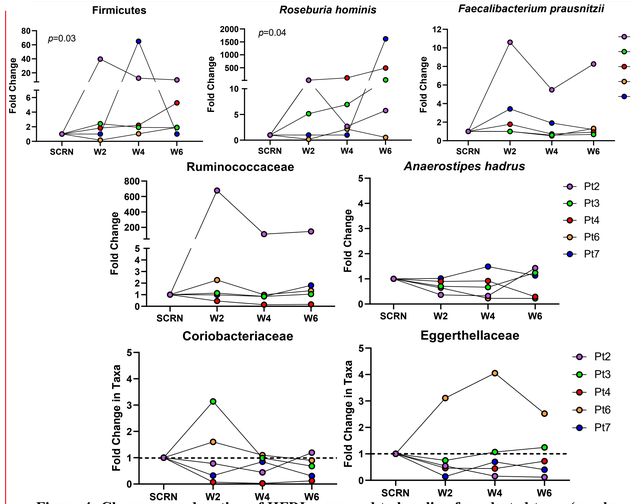
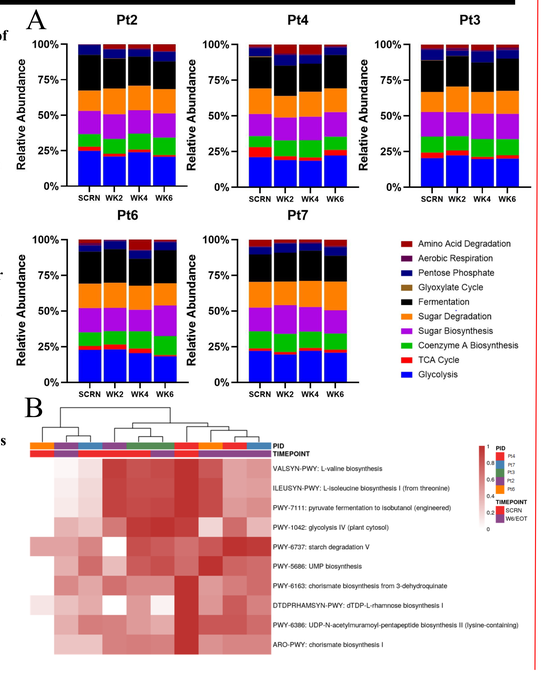


Figure 4: Change over duration of HFDI compared to baseline for selected taxa. (p value, calculated based on SCRN vs W6)

Overall Relative Abundance of Preselected Carbohydrate and Amino Acid Metabolism Pathways Remained Stable Across the HFDI

Figure 5: A. Subcategories of fiber-related carbohydrate-processing pathways were measured in relative abundance as a percentage of the total fiber-related carbohydrate-processing metabolome for each patient at each timepoint. B. Heatmap displaying change in relative abundance of specific pathways across patients from screening to week 6.



Shifts in the Relative Abundance of Carbohydrate-Pathways during HFDI Identified From Three Specific Genera

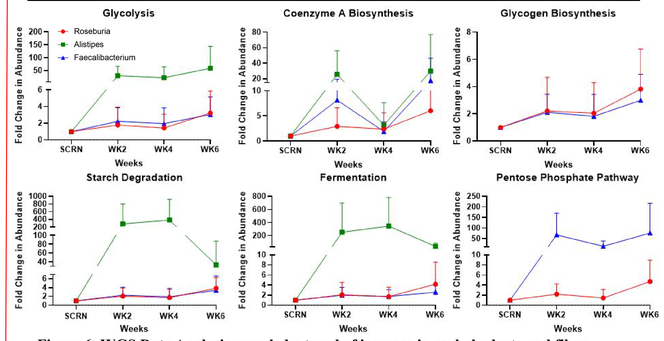


Figure 6: WGS Data Analysis revealed a trend of increase in carbohydrate and fiber-related pathways in three specific genera: *Roseburia*, *Alistipes*, and *Faecalibacterium*. Alistipes did not have pathway abundance data for Glycogen Biosynthesis and the Pentose Phosphate Pathway

Results

- **A HFDI was well-tolerated and feasible in a melanoma population**
- **Baseline microbiome taxonomic bacterial composition was expectedly heterogenous across five participants.**
- **Taxonomic changes upon the HFDI were diverse.**
- **Baseline microbiome pathway abundance of carbohydrate-processing pathways was similar across participants despite taxonomic heterogeneity, reflecting that these are basic housekeeping functions of the gut microbiota.**
- **Carbohydrate processing pathways showed trends to increase for three specific genera: *Roseburia*, *Alistipes*, and *Faecalibacterium***

Conclusion

- **Our data suggested that fiber may induce a promotion of fiber-related carbohydrate-processing pathways in specific genera, not the entire gut microbiome. Fiber may affect the host as shown in other studies via the genera *Roseburia*, *Alistipes*, and *Faecalibacterium*. Further studies are needed to link these genera/pathways to host immunity, as well as look specifically at genes for CAZymes (Carbohydrate-Active Enzymes) involved in individual pathways that make up larger carbohydrate-processing pathways**

References

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