Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response


RESEARCH

Gut bacteria modulate the response to immune checkpoint blockade (ICB) treatment in cancer, but the effect of diet and probiotics on this interaction is not well studied. We assessed the effects of dietary fiber profiles, dietary habits, and commercially available probiotic supplement use in melanoma patients and performed parallel preclinical studies. Higher dietary fiber was associated with significantly improved progression-free survival in 128 patients on ICB, with the most pronounced benefit observed in patients with sufficient dietary fiber intake and no probiotic use. Findings were recapitulated in preclinical models, which demonstrated impaired treatment response to anti–PD-1-based therapy in mice receiving a low-fiber diet or probiotics, with a lower frequency of interferon-γ–positive cytotoxic T cells in the tumor microenvironment. Together, these data have clinical implications for patients receiving ICB for cancer.

Treatment with immune checkpoint blockade (ICB) has revolutionized cancer therapy (1), and the influence of the gut microbiome on therapeutic response has now been demonstrated in numerous human cohorts and in preclinical models (2–7). The human gut microbiome is itself shaped by a wide variety of environmental exposures, including diet (8, 9) and medication use (10–13), with host genetics accounting for <10% of variation (14). However, whether factors such as dietary fiber intake and the use of commercially available probiotics affect immunotherapy responses in cancer patients remains unclear.

To help address this, we profiled the gut (fecal) microbiome and assessed clinicopathologic features and outcomes in a large cohort of melanoma patients (n = 438; Fig. 1A and fig. S1). The majority of these patients were receiving systemic therapy for metastatic melanoma (n = 321), and responses to treatment were assessed with radiographic imaging in those with evaluable treatment responses (n = 293), classifying patients as either responders ([R] complete or partial response or stable disease ≥6 months; n = 193) or nonresponders ([NR] stable disease <6 months or progressive disease; n = 100) using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (15). The majority of patients were treated with ICB (87%), most commonly anti–PD-1 programmed cell death 1 (anti–PD-1) therapy (Fig. 1A, fig. S1, and table S1). Patients initiating therapy with ICB were asked to co-enroll onto a lifestyle survey protocol, which included baseline assessments of dietary habits and use of probiotic supplements within the past month (n = 158; Fig. 1A, fig. S1, and table S1) (16, 17).

We first assessed the relative abundance of gut microbial taxa associated with response to anti–PD-1 immunotherapy in our prior published study (4) within a larger cohort of newly accrued anti–PD-1–treated patients (n = 132 total; n = 87 R and n = 45 NR), excluding patients from the previously published cohort. On the basis of our prior study, we hypothesized that bacteria from the Ruminococcaceae family and Faecalibacterium genus would be associated with response to therapy. We tested this by specifically querying the abundance of these taxa in responders versus nonresponders to anti–PD-1, again observing enrichment of both taxa (Fig. 1B) as well as of Faecalibacterium prausnitzii in the metagenomic subset (n = 111 total; n = 71 R and n = 40 NR; fig. S2A) in anti–PD-1 responders. We did not observe significant differences in the alpha and beta diversity of the gut microbiota in responders versus nonresponders (fig. S2, E and F), in contrast to our prior study. This discrepancy may reflect associations driven by a small number of patients in the prior study with improved power and reduced error in the larger cohort (fig. S3 and tables S2 to S4), and it underscores the lack of concordance across numerous studies that implicate gut bacteria in response to cancer immunotherapy (18).

Next, we assessed the composition of the gut microbiome in responders and nonresponders in the full cohort of late-stage melanoma patients with evaluable responses to any systemic therapy (n = 293 total; n = 193 R and n = 100 NR; Fig. 1C), as well as in all patients treated with anti–PD-1 monotherapy (fig. S2), including patients from both the newly accrued and the previously published cohorts. Across the full cohort, we observed a significantly higher abundance of Ruminococcaceae in the gut microbiota of responders versus nonresponders treated with anti–PD-1 or other systemic therapies that remained consistent after adjustment for potential confounders [age, sex, body mass index (BMI), prior treatment, and antibiotic use] (Fig. 1C, fig. S2, and tables S5 to S9). However, we did not observe significant differences in the overall composition of the gut microbiota in responders versus nonresponders in this larger cohort of patients on systemic therapy (fig. S2 and table S0), nor was there strong concordance with response-associated taxa from the prior study—beyond Ruminococcaceae—in the newly accrued cohort (figs. S3 and S4 and tables S3 and S10). We also assessed the abundance of our previously reported response-associated taxa in published datasets from two recently completed clinical trials demonstrating potential efficacy of the use of fecal microbiota transplant (FMT) + anti–PD-1 in immunotherapy-refractory melanoma patients (19, 20), noting that many of our response-associated taxa appeared to be enriched in the post-FMT specimens from patients who responded to this treatment (Fig. 1D and E, and fig. S5).

Given that cancer patients are increasingly interested in using probiotic supplements to augment gut health, we assessed the use of commercially available probiotics within our cohort and observed that 31% (49 of 158) of late-stage melanoma patients initiating ICB reported that they had taken a probiotic supplement within the past month. Patients who reported taking a probiotic supplement preceding the start of treatment with ICB had a lower BMI, were less likely to take statins, and reported slightly higher intake of vegetables and legumes than patients who...
did not take probiotic supplements (table S1). The proportion of patients reporting antibiotic use within the past month was markedly similar in those who did (29%) versus did not (28%) report probiotic use. Steroid or proton-pump inhibitor use was also not associated with probiotic use (table S1). We then assessed whether probiotic use was associated with differential outcomes in patients treated with ICB and observed no statistically significant differences in progression-free survival (PFS) (n = 158; Fig. 2A; median PFS 17 versus 23 months; Table 1) or odds of response in patients who reported taking probiotics (59% R) versus those who did not (68% R) (Table 1 and tables S1, S11, and S12). The modest associations of probiotic use and outcomes in this cohort were not surprising to us because limitations existed regarding the overall cohort size, as well as substantial heterogeneity in the specific probiotic supplement(s) reportedly used by patients. Although we did not observe statistically significant differences in outcomes or in microbiota features (fig. S6 and table S9) in patients on ICB by probiotic use, the overall trends observed were intriguing—particularly given the relatively high proportion of patients reporting probiotic supplementation in this cohort. Thus, we sought to examine the effects of probiotic use on response to ICB in preclinical models.

To do this, gemp-reve mice first received FMT using donor stool from a complete responder (CR) patient to anti–PD-1 blockade. After this, mice were orally gavaged with one of two commercially purchased probiotics (*Bifidobacterium longum*– or *Lactobacillus rhamnosus* GG–based) versus sterile water control. Viability and composition of the bacterial strains in the probiotic were confirmed by culture and sequencing (fig. S7). Mice were then challenged with murine melanoma tumors and treated with anti–PD-1 ligand 1 (anti–PD-L1) therapy (because treatment with this antibody is more effective in this particular murine tumor model than anti–PD-1) (Fig. 2B). In these studies, mice receiving probiotics demonstrated impaired antitumor response to treatment with anti–PD-L1 and had significantly larger tumors compared with control mice (Fig. 2C), with findings that were recapitulated in an additional murine tumor model (fig. S8). Notably, similar findings were also observed in non–germ-free and specific pathogen-free (SPF) mice implanted with melanoma tumors (fig. S8) that harbor a microbiota from birth to which they are well colonized.

We next compared the gut microbiota of mice receiving probiotics versus sterile water control, and we observed differences in gut microbiota diversity in the mice receiving probiotics compared with control (Fig. 2D and E, and fig. S9). Analysis of tumor-infiltrating immune subsets from anti–PD-L1–treated mice revealed a significantly reduced frequency of interferon-γ (IFN-γ) positive CD8 T cells in tumors of probiotic-treated mice versus controls (Fig. 2F). A trend toward fewer IFN-γ CD4 T helper 1 (T(H)1) cells in tumors from mice receiving probiotics versus control was also observed, although this did not reach statistical significance (Fig. 2G). Unsupervised analyses of the flow cytometry data corroborated the findings in immune subsets between probiotic treatment versus control, demonstrating a reduced frequency of cytotoxic T cells in the tumor microenvironment of probiotic-treated mice (Fig. 2H). These data are in line with previously published studies that have demonstrated increased tumorigenesis in murine models of colorectal carcinoma in probiotic-treated mice (22), although other studies have shown a beneficial effect of other probiotic formulations and rationally designed bacterial consortia in preclinical models and patient cohorts (22–24).

Given that many of the response-associated bacteria identified in our cohort have known roles in starch degradation and fiber fermentation (25–29), we next sought to assess the effect of dietary fiber intake on response to ICB. We asked patients who were initiating treatment with ICB to complete the National Cancer Institute Dietary Screener Questionnaire (NCI-DSQ) (17), and responses were scored to derive dietary fiber intake from 26 queried food items. Dietary fiber intake was assessed per 5-g/day incremental increase and further categorized according to the distribution of reported intake within our cohort with low or insufficient fiber intake corresponding to <20 g/day and sufficiently high fiber intake at or above 20 g/day, a threshold met by ~30% (37 of 128) of ICB patients (Fig. 3A and fig. S10A). As expected, dietary fiber intake was highly correlated with fruit, vegetable, legume, and whole grain intake and, to a lesser extent, with calcium intake (fig. S10B and table S1). Patients with insufficient dietary fiber intake were more likely to be obese—a factor that we and others have previously...
Fig. 1. Profiles of gut microbiota in patients with melanoma and associations with outcomes on therapy. (A) Schema of study design. (B) Box plots comparing the relative abundance of anti–PD-1 response–associated taxa from Gopalakrishnan et al. (4) with a newly recruited cohort (n = 132) of anti–PD-1–treated patients (P = 0.036 and P = 0.018, respectively, for Ruminococcaceae and Faecalibacterium by Wilcoxon rank sum test). Patients included in the prior...
found to be paradoxically associated with improved response to ICB (30, 31)—and were also more likely to take antihypertensive medications (table S1).

Patients who reported sufficient dietary fiber intake ($n = 37$ of 128) demonstrated improved PFS over those with insufficient dietary fiber intake (median PFS not reached versus 13 months; Fig. 3A and Table 1). After adjustment for clinical factors, every 5-g increase in daily dietary fiber intake corresponded with a 30% lower risk of progression or death (Table 1). Similar associations were observed when assessing dietary fiber intake in relation to the odds of response to ICB (Table 1). The observed protective effect of dietary fiber intake in relation to PFS and response remained consistent among the subset of patients treated with anti–PD-1 monotherapy, with the exclusion of patients reporting recent antibiotic use and no probiotic use compared with all other groups (median PFS not reached versus 13 months; Fig. 3B and Table 1). Similar positive associations were observed for ICB response in patients reporting sufficient dietary fiber intake and no probiotic use compared with all other groups ($n = 123$; 82 versus 59% responders; Table 1 and tables S11 and S12). Microbial alpha diversity and Ruminococcaceae family and Faecalibacterium genus abundances were also numerically higher in patients with sufficient dietary fiber intake and no probiotic use, although only 18% of patients met these criteria and results did not reach statistical significance (fig. S12).

Intrigued by these findings, we next examined whether dietary fiber modulation could enhance therapeutic response to ICB in preclinical melanoma models. In these studies, conventionally housed C57BL6 SPF mice were provided with a standard fiber-rich whole grain diet (17.6% fiber) versus a fiber-poor diet (2% fiber) (29), challenged with murine melanoma tumors (35), and treated with anti–PD-1 therapy versus isotype control (Fig. 3C). Mice receiving a fiber-rich diet demonstrated delayed tumor outgrowth compared with mice who received a fiber-poor diet when treated with anti–PD-1 (Fig. 3D). These findings were recapitulated in additional tumor models (figs. S13 and S14). By contrast, there was no effect of fiber-rich versus fiber-poor diet on the response to anti–PD-1 therapy in germ-free mice, which supports the hypothesis that the effect of this dietary intervention on treatment efficacy is microbiota dependent (fig. S13). Profiling of the gut microbiome revealed significant differences in the community structure of mice fed fiber-rich versus fiber-poor diets (Fig. 3E) and taxonomic differences between the groups (fig. S15).

Stool metabolomic profiling also revealed significantly higher levels of the short chain fatty acid (SCFA) propionate in mice receiving a fiber-rich diet, although no significant differences were noted in SCFA levels as a whole (fig. S16). Immune profiling by flow cytometry of tumors in treated mice revealed a significantly higher frequency of CD4+ T cells overall (and those expressing PD-1) in the tumors of mice on high-versus low-fiber diets (fig. S17, A and B). We next conducted RNA sequencing of CD4+ tumor-infiltrating lymphocytes (TILs) and observed significantly higher expression of genes related to T cell activation and interferon response in mice receiving a high-versus low-fiber diet in the setting of treatment with anti–PD-1 (Fig. 3, F and G, and tables S13 and S14). Further, network analysis of murine data suggested that the fiber-fermenting Ruminococcaceae family of bacteria may contribute to the effects of fiber on antitumor immunity by affecting pathways of T cell activation as well as the accumulation of T cells in the tumor, including inducible T cell co-stimulator (ICOS)-expressing CD8+ and CD4+ T cells (fig. S17, C to H).

Together, these data have important implications. We show that dietary fiber and probiotic use, factors known to affect the gut microbiome, are associated with differential outcomes to ICB. Although causality cannot be addressed from the observational human cohort, where unmeasured confounders may exist, our preclinical models support the hypothesis that dietary fiber and probiotics modulate the microbiome and that antitumor immunity is impaired in mice receiving a low-fiber diet and in those receiving probiotics—with suppression of intratumoral IFN-γ T cell responses in both cases.

Numerous challenges exist to decipher how best to leverage the microbiome to optimize patient outcomes, starting with what to target—selected features or community function—and whether this can be safely achieved through supplementation or more comprehensive dietary approaches. Several prior studies have shown that controlled increases in dietary fiber intake can modulate the gut microbiome but also that interindividual variation in the gut microbiome drives differential effects of specific fibers (and prebiotics) on host metabolism.
Fig. 2. Effect of probiotic supplement use in patients and in preclinical models of melanoma immunotherapy. (A) Kaplan-Meier plot comparing progression-free survival intervals by probiotic use among patients who received ICB \((n = 158; \ P = 0.29 \text{ by log-rank test})\). (B) Experimental design of studies in germ-free (GF) mice that received FMT from a complete responder (CR) donor combined with probiotic 1, probiotic 2, or sterile water control before tumor injection \([2.5 \times 10^5 \text{ to } 8 \times 10^5 \text{ BRAF}^{G60E/PTEN}^{-/-} \text{ (BP) tumor cells}]\) and treatment with anti–PD-L1. Time is in days relative to tumor injection [day 0 (D0)]. PO, per orem; s.c, subcutaneous; IP, intraperitoneal. (C) Mouse tumor growth curves comparing volume of tumors in mice who received probiotics or
sterile water control (n = 4 to 5 per group); probiotic 1 versus probiotic 2 versus sterile water control. Data are means ± SEM tumor volume. All P values are from a likelihood ratio test in a linear mixed model (P = 0.04 Bifidobacterium longum 35624–based probiotic 1 versus control; P = 0.01 Lactobacillus rhamnosus GG–based probiotic 2 versus control). *P < 0.05. (D) Box plots comparing alpha diversity of the gut microbiome, as measured by the inverse Simpson index in mice treated with control, probiotic 1 (Bifidobacterium longum 35624–based), or probiotic 2 (Lactobacillus rhamnosus GG–based) (pairwise P values compared with control were calculated with Wilcoxon rank sum test). Fecal samples were collected for microbiome analysis (via metagenomic sequencing) from tumor-bearing mice before the anti–PD-L1 therapy (n = 7 to 8 per group), mimicking baseline sample collection from patients. (E) Ordination plot by t-distributed manifold approximation and projection (t–UMAP) by Bray-Curtis distance, demonstrating compositional differences of the gut microbiome in mice treated with sterile water control, probiotic 1 (Bifidobacterium longum 35624–based), or probiotic 2 (Lactobacillus rhamnosus GG–based) [permutational multivariate analysis of variance (PERMANOVA) P = 0.036]. (F and G) Pairwise comparisons of sterile water control versus probiotic 1 (Bifidobacterium longum 35624–based) or control versus probiotic 2 (Lactobacillus rhamnosus GG–based) groups (n = 6 per group) via supervised analysis with manual gating for either frequency of IFN-γ+ CD8+ T cells in tumors (percent total tumor CD8+ T cells) (P = 0.03, P = 0.03) (F) or frequency of IFN-γ+ CD4+ T cells in tumors (percent total tumor CD4+ T cells) (P = 0.26, P = 0.10) (G). (H) Unsupervised analysis of flow cytometry data showing density t-distributed stochastic neighbor embedding (t–SNE) plot of tumor-infiltrating immune cells overlaid with color-coded clusters, with an equal number of CD45+ infiltrating leukocytes for each treatment group (control, probiotic 1, and probiotic 2).

### Table 1. Associations of baseline probiotic supplement use and dietary fiber intake in late-stage melanoma patients treated with ICB and followed for tumor response and progression-free survival.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>n</th>
<th>Progression-free survival</th>
<th>Odds of response to ICB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Events</td>
<td>Median months</td>
</tr>
<tr>
<td>Probiotic supplement use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>158</td>
<td>85</td>
<td>23</td>
</tr>
<tr>
<td>No</td>
<td>109</td>
<td>56</td>
<td>17</td>
</tr>
<tr>
<td>Yes</td>
<td>49</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Dietary fiber intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>128</td>
<td>73</td>
<td>13</td>
</tr>
<tr>
<td>Per 5 g/day increase</td>
<td>91</td>
<td>57</td>
<td>13</td>
</tr>
<tr>
<td>Insufficient</td>
<td>12</td>
<td>6</td>
<td>N/R</td>
</tr>
<tr>
<td>Sufficient</td>
<td>37</td>
<td>16</td>
<td>N/R</td>
</tr>
<tr>
<td>Dietary fiber intake + probiotic supplement use</td>
<td>123</td>
<td>72</td>
<td>13</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>72</td>
<td>13</td>
</tr>
<tr>
<td>Sufficient + no probiotics</td>
<td>22</td>
<td>8</td>
<td>N/R</td>
</tr>
<tr>
<td>Other†</td>
<td>101</td>
<td>64</td>
<td>13</td>
</tr>
</tbody>
</table>

*HR and 95% CI estimated using Cox proportional hazards regression. OR and 95% CI estimated using logistic regression. All models include multivariable adjustment for subtype, stage, lactate dehydrogenase level, and BMI. †P value by Wald test.

†Other category includes patients who either reported insufficient fiber intake or probiotic use.

(36–40). Ongoing dietary intervention studies in the setting of ICB are critical for establishing whether a targeted and achievable diet change at the initiation of ICB can safely and effectively improve outcomes (NCT04645680). Although our findings suggest that undirected use of commercially available probiotics may be harmful in the setting of ICB, further study of rationally designed and targeted probiotics or bacterial consortia is warranted on the basis of promising early data of this approach (22–24).

Some analyses in the current cohort were not adequately powered to assess the full effect of these factors, and further validation is needed in independent cohorts with more in-depth and detailed assessment of dietary intake and the use of specific probiotic supplements, along with further mechanistic studies in preclinical models. Nonetheless, these notable (and perhaps unexpected) findings from studies in this observational patient cohort are corroborated by parallel studies in preclinical models with preliminary mechanistic insights. In light of these collective results, dietary habits and probiotic supplement use should be considered in patients receiving ICB and in efforts to modulate the gut microbiota. These factors should be more thoughtfully evaluated in strategies to improve cancer outcomes.

### REFERENCES AND NOTES

A. Dietary Fiber Intake

Survival probability

- Sufficient fiber
- Insufficient fiber

p = 0.047

Time (months)

Number at risk

37 (29%) 15 8 0

91 (71%) 33 7 1

B. Dietary Fiber Intake and Probiotic Use

Survival probability

- Sufficient fiber, no Probiotics
- Insufficient fiber, no Probiotics
- Sufficient fiber, Probiotics
- Insufficient fiber, Probiotics

p = 0.11; a vs. b = 0.015

Number at risk

22 (18%) 13 6 1

65 (53%) 22 5 0

12 (10%) 1 1 0

24 (19%) 9 3 0

C. Tumor Injection

D0 - D7 - D10 - D13 - D16

1 x 10^6 cells

Anti-PD1 (250 µg/mouse) or isotype control

Females C57BL/6 SPF

D. Tumor size (mm^3)

Days after treatment

E. UMAP 1 vs. UMAP 2

PERMANOVA p = 0.001

F. Gene Expression of CD45+ Tumor Infiltrating Cells

G. -log10(p) gene set

mmu04660: T cell receptor signaling pathway
mmu04211: T cell activation
mmu003441: response to interferon-gamma
mmu002693: negative regulation of immune system
mmu02250: adaptive immune response
mmu04083: immunoregulatory interactions between lymphoid and non-lymphoid cells
mmu0071901: negative regulation of protein serine/threonine kinase activity
mmu0050854: regulation of antigen receptor-mediated signaling pathway
mmu04612: Antigen processing and presentation
mmu0050902: leukocyte migration
mmu004514: Cell adhesion molecules (CAMs)
mmu0051345: positive regulation of hydrolase activity
mmu004658: Th17 differentiation
mmu0042987: amyloid precursor protein catabolic process
mmu0045596: negative regulation of cell differentiation
mmu00229481: FCGR activation
mmu0070838: divalent metal ion transport
mmu0071887: leukocyte apoptotic process
mmu0034393: positive regulation of smooth muscle cell apoptotic process
mmu0051482: positive regulation of cytosolic calcium ion concentration involved in phospholipase C
37. A. Oliver et al., mSystems 6, e00123-21 (2021).

Acknowledgments
C.N.S. acknowledges the Parker Institute for Cancer Immunotherapy for funding time devoted to continued analysis of metabolomics. She also acknowledges M. D. Swartz, L. Piller, and X. Du at UTSPH for their participation on their thesis committee. J.L.M. acknowledges the Transdisciplinary Research in Energetics and Cancer Research Training Workshop R25CA203650, J.L.M. and C.R.D. acknowledge the MDACC Center for Energy Balance in Cancer Prevention and Survivorship. C.R.D. acknowledges the MDACC Bionutrition Core. We thank our collaborators and personnel at the ICI, NCI Microbiome and Genetics Core Facility, and NCI Mouse Gnotobiotic Core Facility. The Aleck Center for Metabolomics and the Melanoma Associated Microbiome and Translational Research (PRIME-TR) for supporting the analysis and interpretation of the microbiome results presented herein (J.A.W. and N.J.A. are the program director and executive scientific director for PRIME-TR, respectively). Most of the authors would like to thank all who contributed their time, samples, and data to this research.

Funding: This study received support from National Institute of Health grant R01 CA215996-01A1 (J.A.W.); US-Israel Binational Science Foundation grant 203332 (J.A.W.); the Melanoma Research Alliance 40122024 (J.A.W.); American Association for Cancer Research Grant to Stand Up to Cancer grant SU20-AACR-IRG-19-17 (J.A.W.); the Andrew Sabin Family Fellows Program (J.A.W. and C.R.D.); MD Anderson Cancer Center’s Melanoma Molecular Targets and Pharmacology Program (J.A.W., L.C., C.R.D., M.A.D., S.S.W., R.R.J., and E.M.B.); and the Melanoma Research Alliance grant 544449 (L.C., J.A.W., and J.L.M.). The authors additionally received support from Department of Defense grant W81XWH 16 1 012 (J.A.W.); the MD Anderson Cancer Center Multidisciplinary Research Program grant (J.A.W.); the Parker Institute for Cancer Immunotherapy at MD Anderson Cancer Center (J.A.W., H.A.T., P.S., and J.P.A.); American Society of Clinical Oncology and Conquer Cancer Foundation Career Development award AWD0000567 (J.L.M.); the Ekins Foundation Grant to the Seearve Foundation (J.L.M.); the Rising Tide Foundation Grant AWD00004505 (J.L.M.); the Mark Foundation grant AWD00004538 (J.L.M.); the Longenbaugh-Torian Fund (J.L.M.); the MD Anderson Cancer Center SPORE in Melanoma P50CA163620, J.A.W., L.C., T.G., H.C., Y.Y., and C.H.; the National Institutes of Health (NIH) grants R01AI109294 (S.S.W.); National Institute of Health grant R01AI143886 (J.H.); Columbia University Health Sciences NCI Cancer Center Support grant P30 CA036666 (J.H.); National Institute of Health grant R01HL214132 (R.R.J.); Cancer Prevention and Research Institute of Texas Research Training Program RP160097 (X.Z.); National Health and Medical Research Council of Australia CI Martin Early Career Fellowship grant 1149880 (M.A.C.); National Institutes of Health T32 CA 092174 (J.E.G., J.A.W., and B.A.H.); the National Institute of Health Career Development Award 5K01 CA230467 (M.G.W.); the National Cancer Institute Center for Cancer Research grant 1P01CA224070-03 (M.G.W.); the National Institute of Health grant 1R01AI09924 (S.S.W.); National Institute of Health grant 1R01AI133822 (S.S.W.); the Richard E. Haynes Distinguished Professor in Clinical Cancer Prevention (L.C.); American Cancer Society grant RSG-17-041-01-DOD (C.R.D.); the National Institute of Health Intramural Research Program (E.P., C.P.D., and G.M.E.); FLEX Synergy Award from the National Cancer Institute for Cancer Research (E.P., C.P.D., and G.M.E.); the National Institute of Health Intramural Research Program (J.A.M., M.V., J.H.B., R.R.J., and G.T.); the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (M.A.D.); American Cancer Society/ Melanoma Research Alliance grant 134438-MRT-19-168-01 (M.A.D.); the AIM at Melanoma Foundation (M.A.D.); the National Institute of Health grant 1R01AI09924 (S.S.W.); the National Institute of Health Intramural Research Program (J.A.M., M.V., J.H.B., R.R.J., and G.T.); the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (M.A.D.); American Cancer Society/ Melanoma Research Alliance grant 134438-MRT-19-168-01 (M.A.D.); the AIM at Melanoma Foundation (M.A.D.); the National Institute of Health/ National Cancer Institute grant 1U54CA224070-03 (M.A.D.); Cancer Fighters of Houston (M.A.D.); and the Anne and John Mendelsohn Chair for Cancer Research (M.A.D.).


Competing interests: None declared.
Pharma, LISCure Biosciences, and Prolacta Biosciences; and consults for Davolterra, Merck, Microbiome DX, and Karius. C.H. is on the scientific advisory board for Seres Therapeutics and Empress Therapeutics. M.K.W. is on the advisory boards of Merck, Pfizer, Bristol Myers Squibb, Regeneron, EMD-Serono, EvCure, Castle Biosciences, and Adagene. H.A.T. is a consultant for BMS, Merck, Novartis, Genentech, Eisai, Iovance, Karyopharm, and Pfizer and reports research funding to institution from BMS, Merck, Novartis, Genentech, GSK, and Venn Biosciences. M.A.D. has been a consultant to Roche/Genentech, Array, Pfizer, Novartis, BMS, GSK, Sanofi-Aventis, VaccineX, Arixigen, Eisai, and ABM Therapeutics, and he has been the principal investigator of research grants to MD Anderson from Roche/Genentech, GSK, Sanofi-Aventis, Merck, Myriad, and Oncothyreon. P.H. is on the scientific advisory board for Dragonfly and Immatics. M.I.R. is on the melanoma advisory board for Merck and is a paid consultant for AMDEN and Merck. S.P.P. reports institutional clinical trial support from NCI, Merck, and Bristol Myers Squibb during the conduct of the study; institutional clinical trial support from Resta Pharmaceuticals, Novartis, Deciphera, Prolectus Biopharmaceuticals, Foghorn Therapeutics, TriSalus Life Sciences, and Seattle Genetics; advisory board honoraria from Castle Biosciences and TriSalus Life Sciences; honoraria as Peer Discussion Group Leader for Merck; and honoraria for service as Chair of International Data Monitoring Committee for Immunocore.

Data and materials availability: Raw sequencing data and all relevant human data necessary for reproducing results are available in the NCBI Sequence Read Archive under BioProject ID PRJNA770295. All analyzed sequencing data are available in the supplementary materials.

SUPPLEMENTARY MATERIALS

science.org/doi/10.1126/science.aaz7015
Materials and Methods
Figs. S1 to S18
Tables S1 to S14
References (41–74)
MDAR Reproducibility Checklist
View/request a protocol for this paper from Bio-protocol.

1 October 2019; resubmitted 17 May 2020
Accepted 24 November 2021
10.1126/science.aaz7015
Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response


Science, 374 (6575), .
DOI: 10.1126/science.aaz7015

Another benefit of dietary fiber

The gut microbiome can modulate the immune system and influence the therapeutic response of cancer patients, yet the mechanisms underlying the effects of microbiota are presently unclear. Spencer et al. add to our understanding of how dietary habits affect microbiota and clinical outcomes to immunotherapy. In an observational study, the researchers found that melanoma patients reporting high fiber (prebiotic) consumption had a better response to checkpoint inhibitor immunotherapy compared with those patients reporting a low-fiber diet. The most marked benefit was observed for those patients reporting a combination of high fiber consumption and no use of over-the-counter probiotic supplements. These findings provide early insights as to how diet-related factors may influence the immune response. —PNK

View the article online
https://www.science.org/doi/10.1126/science.aaz7015

Permissions
https://www.science.org/help/reprints-and-permissions

Use of this article is subject to the Terms of service

Science (ISSN ) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title Science is a registered trademark of AAAS.
Copyright © 2021 The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science. No claim to original U.S. Government Works