

Diet conditions the gut microbiome for cancer immunotherapy

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Received: August 4, 2026; Accepted: October 22, 2026; Published Online: October 24, 2026; <https://doi.org/10.59717/j.xinn-nutri.2026.100045>

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Citation: Sun F. and Fu T. (2026). Diet conditions the gut microbiome for cancer immunotherapy. *The Innovation Nutrition* 1:100045.

A higher body mass index (BMI) is generally associated with adverse cancer outcomes, yet patients with overweight or obesity can show unexpectedly greater benefit from immune checkpoint inhibitors (ICIs). This "obesity paradox" has remained difficult to interpret because BMI integrates dietary exposure, adiposity, metabolic dysfunction, inflammation and the gut microbiome. In a recent Nature study, Desharnais and colleagues disentangle these variables using 12 compositionally distinct mouse diets and show that anti-PD-1 efficacy is better explained by the diet–gut axis than by body weight or metabolic dysfunction alone.¹ The study then follows this association through short-term diet switching, faecal microbiota transplantation (FMT), single-strain and germ-free experiments, metabolomics and human validation, providing a direct view of how dietary context conditions microbial function during immunotherapy (Figure 1).

DIET SEPARATES IMMUNOTHERAPY RESPONSE FROM OBESITY

The initial dietary screen is central to the study. After 15 weeks, the 12 diets generated a broad spectrum of body weight, adiposity, glucose tolerance, insulin, leptin and immune phenotypes. Yet anti-PD-1 efficacy in the HKP1 lung cancer model did not correlate with body weight, fat mass, glucose tolerance, insulin, leptin or a composite metabolic score. Four of six obesity-inducing diets supported anti-PD-1 responses, compared with two of six non-obesogenic diets. The exceptions are informative: the lean Inulin group was responsive, whereas the Mediterranean diet caused weight gain but remained non-responsive. Thus, obesity was neither necessary nor sufficient for treatment benefit. These findings refine, rather than negate, clinical associations between higher BMI and ICI outcome,² suggesting that BMI may capture diet-linked biological states without identifying the mechanisms responsible for them.

Microbial and immune features further separated responder from non-responder diets. Lactobacillaceae, particularly *Lactobacillus*, were enriched in several responder conditions, whereas Bacteroidaceae and Sutterellaceae were enriched in non-responders. This was not a universal taxonomic rule: Inulin was responsive despite low *Lactobacillus* abundance. The tumour immune compartment also differed. Responders had greater intratumoural CD3+ T-cell abundance, whereas non-responders showed more Ly6G+ neutrophils, higher neutrophil-to-T-cell ratios and a greater proportion of PD-1+Ki-67- cells within both CD4+ and CD8+ T-cell compartments, a phenotype the authors describe as resting or non-proliferative. Importantly, microbiome composition was largely established after only three weeks of diet exposure, before the larger weight differences that developed by 15 weeks, and the High Fat and Psyllium diets retained their responder and non-responder phenotypes across lung cancer and melanoma models. Broad-spectrum antibiotics altered tumour growth in most obesogenic models; in the High Fat setting, continuous antibiotics also removed anti-PD-1 sensitivity. The Ketogenic model was an important exception, indicating that microbiome dependence is substantial but not uniform across diets.

DIET RAPIDLY REDIRECTS MICROBIAL FUNCTION AND FMT OUTCOME

The short-term switch experiments make the dietary effect especially clear. Changing mice from the non-responder Psyllium diet to the responder High Fat diet only 48 hours before anti-PD-1 treatment was sufficient to restore sensitivity, whereas the reciprocal switch removed it. T-cell infiltration itself did not differ between switch conditions, but intratumoural CD4+ and CD8+ T cells showed improved functional status, including increased IFN γ and TNF production. At the same time, faecal *Lactobacillus* increased and *Bacteroides* decreased within 48 hours. The speed of these changes separates diet-conditioned microbial and immune effects from the slower devel-

opment of obesity.

The FMT experiments extend this principle from endogenous communities to transplanted microbiota. High Fat-fed mice remained sensitive to anti-PD-1 after receiving FMT from Psyllium-fed non-responder donors, and the transplanted communities progressively diverged from the donor profile toward the state selected by the recipient diet. The same logic held with human material: stool from an ICI-refractory patient produced resistance in Psyllium-fed recipients but anti-PD-1 sensitivity in High Fat-fed recipients. These findings do not make donor selection irrelevant. Rather, they show that donor microbiota enter a nutritional environment that can reshape their abundance and function. This provides a mechanistic reason to consider recipient diet alongside donor composition in microbiome-based ICI interventions, including FMT approaches that have already shown activity in ICI-refractory disease.³ Recent evidence that diet can outperform microbial transplantation during microbiome recovery supports the same ecological principle.⁴

The study then asks whether a specific responder-associated organism can reproduce this diet dependence. Metagenomic analysis identified *Lactobacillus johnsonii* as the species most enriched in obesity-associated responder diets. In germ-free mice, *L. johnsonii* combined with the High Fat diet produced the strongest anti-PD-1 effect and tumour clearance. By contrast, *L. johnsonii* with Psyllium or the non-responder-associated *Muribaculum gordoncarteri* with High Fat produced only partial sensitivity. The key result is therefore not that one bacterium is universally beneficial, but that microbial identity and dietary context interact. Consistent with this interpretation, the authors emphasize that *L. johnsonii* is unlikely to be the sole organism capable of generating the relevant metabolic activity and that other taxa or consortia may support similar, or counter-regulatory, pathways.

AROMATIC AMINO ACID METABOLISM LINKS DIET, MICROBES AND T-CELL FUNCTION

Untargeted serum metabolomics next identified aromatic amino acid metabolism, particularly tryptophan- and tyrosine-derived pathways, as a prominent feature of obesogenic responder diets. The authors initially focused on indole-3-lactic acid (ILA), a tryptophan-derived metabolite associated with *Lactobacillus* biology in other tumour settings. ILA was enriched in responder diets and altered PD-1, Ki-67, IFN γ and granzyme B during *ex vivo* T-cell stimulation. However, ILA was undetectable in serum from responding *L. johnsonii*-monocolonized mice, arguing that it could not directly explain the diet-*L. johnsonii* interaction in this model.

This led the authors to broaden the search and identify desaminotyrosine (DAT; 3-(4-hydroxyphenyl)propionic acid), a microbiota-derived phenylpropionate produced during tyrosine metabolism. DAT was higher in *L. johnsonii*-monocolonized mice fed High Fat than in those fed Psyllium, remained low in germ-free mice fed High Fat without *L. johnsonii* and was modestly increased in live *L. johnsonii* culture supernatants. Functionally, DAT enhanced CD8+ T-cell effector cytokine production *ex vivo*. More importantly, DAT supplementation sensitized Psyllium-fed mice to anti-PD-1 *in vivo*. These experiments establish DAT as one functional mediator of the diet-microbiome interaction, consistent with previous evidence linking DAT to T-cell priming during checkpoint blockade,⁵ while leaving room for complementary indole and phenylpropionate pathways.

Two human experiments provide a translational bridge. In plasma from 53 patients with non-small-cell lung cancer receiving ICI, responders showed higher levels of ILA and 3-hydroxy-3-(3-hydroxyphenyl)propionic acid-O-sulfate, a host-conjugated downstream correlate within the DAT-related phenylpropionate axis. Separately, human-to-mouse FMT from six donors

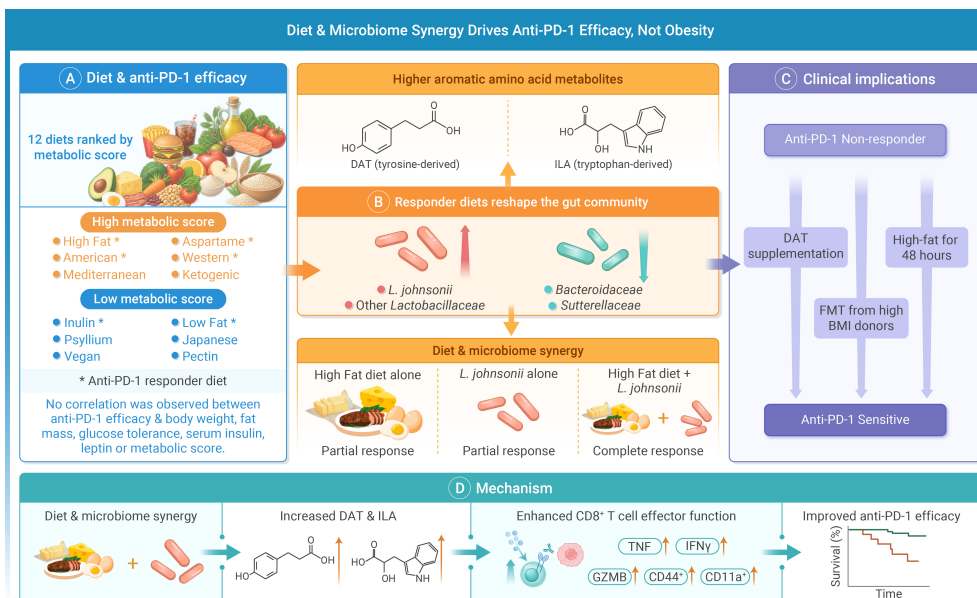


Figure 1. Dietary context, not obesity, shapes microbial metabolism and the anti-PD-1 response (A) Across 12 nutritionally diverse diets ranked by metabolic score, anti-PD-1 efficacy showed no correlation with body weight, fat mass, glucose tolerance, serum insulin, leptin or the composite metabolic score. Responder diets (asterisks) were distributed across both high-metabolic-score (High Fat, American, Western, Aspartame) and low-metabolic-score (Inulin, Low Fat) groups, dissociating the response from adiposity itself. (B) Responder diets reshaped the gut community, enriching *Lactobacillus johnsonii* and other Lactobacillaceae while depleting Bacteroidaceae and Sutterellaceae, and raised aromatic amino acid-derived metabolites: DAT (tyrosine-derived) and ILA (tryptophan-derived). In germ-free mice, the High Fat diet alone or *L. johnsonii* alone produced only partial responses, whereas the combination produced complete responses, demonstrating diet-microbe synergy rather than a universal single-taxon effect. (C) Three interventions converted anti-PD-1 non-responders to a sensitive state: DAT supplementation, a 48-hour switch to the High Fat diet, and FMT from high-BMI donors. (D) Proposed mechanism: diet-microbe synergy increases DAT and ILA, which enhance CD8⁺ T-cell effector function (IFN γ , TNF, GZMB, CD44⁺, CD11a⁺) and improve anti-PD-1 efficacy and survival.

with BMI ≥ 25 produced significant anti-PD-1 sensitivity, whereas FMT from three donors with BMI < 25 did not. The small donor numbers and the inability of BMI to define the underlying diet or microbial function warrant caution, but the convergence of circulating aromatic amino acid metabolites and transmissible donor effects supports the clinical relevance of the pathway identified in mice.

TRANSLATIONAL IMPLICATIONS AND FUTURE DIRECTIONS

The strength of this study lies in its demonstration that dietary context can shape the microbiome, microbial metabolism and antitumour immunity in a coordinated manner, thereby conditioning the response to immune checkpoint blockade independently of body weight or metabolic dysfunction. These findings shift the interpretation of the obesity-immunotherapy association from a host phenotype defined by BMI toward a dynamic diet-microbiome-immune axis. More broadly, they suggest that the therapeutic activity of a microbiome cannot be considered independently of the nutritional environment in which it operates.

This framework has important implications for microbiome-based cancer interventions. Rather than seeking a universally beneficial diet, bacterium or microbial metabolite, future studies should identify nutritional conditions that reproducibly support immunostimulatory microbial functions while avoiding the adverse consequences of chronic obesogenic feeding. The rapid reversibility of the dietary effect further raises the possibility that short-term, compositionally defined dietary interventions could be developed to condition the microbiome before or during immune checkpoint blockade. In parallel, defined bacterial consortia or microbial metabolites such as DAT may provide more controllable approaches to reproduce beneficial microbial functions. For FMT, probiotic and dietary intervention trials, systematic characterization of recipient diet may therefore be as important as profiling the administered microbiota.

Several questions remain before these principles can be translated clinically. Future studies should determine whether the diet-microbiome interaction is conserved across orthotopic and spontaneous tumour models, cancer types and treatment regimens, and should establish which dietary components and microbial functions are necessary and sufficient for therapeutic benefit. Importantly, the relevant biomarkers may ultimately be functional rather than taxonomic, integrating dietary exposure, microbial metabolites and immune state. Such an approach could enable patient-specific nutritional or microbiome interventions designed to enhance ICI efficacy without

relying on obesity itself. Thus, the central lesson of this study is not that a particular diet or bacterium improves immunotherapy, but that nutritional context is an actionable determinant of microbial function and antitumour immunity. This concept provides a rationale for integrating diet into the design, interpretation and clinical development of microbiome-based immunotherapy strategies.

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FUNDING AND ACKNOWLEDGMENTS

F.S. and T.F. acknowledge startup support from the University of Wisconsin-Madison and the University of Wisconsin Carbone Cancer Center. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

F.S. and T.F. wrote and revised the manuscript. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.