RESEARCH PAPER

Gut Microbiome Modulation and Outcomes of Immune Checkpoint Inhibitors in Solid Tumors: A Secondary Qualitative Review

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ABSTRACT

ICI has revolutionized the treatment of solid tumors, but durable response has only been observed in a minority of patients, and traditional biomarkers are not sufficient to explain the heterogeneity. Indeed, an increasing body of translational evidence suggests that the gastrointestinal tract microbiome is not merely correlational but a host determinant that can be remodeled to influence immune tone, treatment response, and toxicity. Synthesizing clinical evidence on gut microbiome modulation in clinical primaries and outcomes of immune checkpoint inhibitors in solid tumors, this secondary qualitative analysis has a thematic focus on response, survival, and mechanistic plausibility. Eligible English language studies based on citation chasing were searched through a structured search of PubMed, Europe PMC, Crossref, and Google Scholar. The findings synthesis involved fifteen primary studies, and theoretical framing and discussion were conducted by a separate review of the literature. Three common patterns were found in the thematic analysis. First, responder phenotypes were repeatedly associated with higher microbial diversity and microbial enrichment, including Akkermansia, Ruminococcaceae, Faecalibacterium, and Bifidobacterium. Second, in certain environments, uncontrolled exposure to antibiotics and, in others, uncontrolled exposure to probiotics seemed to undermine the integrity of the ecological response and the effectiveness of checkpoints, even though confounding is widespread. Third, proactive microbiome engineering using fecal microbiota transplantation, high-fiber diets, and live bacterial products demonstrated a proof of concept that gut microbial communities can be therapeutically manipulated to make them more responsive to checkpoint therapy. They had strengths in methodology, as they employed translational designs that linked stool sequencing to clinical endpoints, but were also limited, particularly by small sample sizes, uneven sequencing platforms, tumor heterogeneity, and insufficient controls for diet, antibiotics, and geography. Altogether, evidence shows that the gut microbiome is biologically plausible and clinically implementable as a controller of checkpoints, and current evidence is too heterogeneous to support simple blanket prescriptions. Interventional trials that are adequately powered and precision microbiome stratification are now prioritized.

Keywords: gut microbiome, immune checkpoint inhibitors, solid tumors, fecal microbiota transplantation, probiotics, dysbiosis, thematic synthesis.

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INTRODUCTION

Checkpoint blockade is now a fundamental treatment approach to melanoma, non-small cell lung cancer, renal cell carcinoma, hepatobiliary malignancies, and multiple other solid tumors; however, a durable benefit is still only achieved by a minority of treated patients. Recent literature highlights that tissue-centered biomarkers, including PD-L1 expression, microsatellite instability, and tissue mutational burden, remain informative, though incomplete, as they fail to capture host-level ecology that frames systemic immunity.[1,2]

Simultaneously, the gut microbiome has transformed from a hypothetical inference into a feasible determinant of immune checkpoint inhibitor efficacy, tolerability, and immunity. Recent syntheses in solid tumors, immune-related adverse events, melanoma, and translational microbiome engineering

all work towards the perception that microbial ecology can dictate efficacy and toxicity.[3-9,13-19] The biological rationale is now strong. The gut microbiota can modulate dendritic cell maturation, antigen presentation, interferon signal transduction, short-chain fatty acid generation, and CD8 T-cell priming. In contrast, microbial and bile acid signaling, as well as intestinal barrier integrity, can also influence immune-related colitis and other toxicities. [3-6,20]

This theoretical rationale of the review is a combination of three interrelated views. The former is the cancer immunity cycle, which describes the efficacy of checkpoints as a product of effective antigen release and presentation, T-cell priming, trafficking, and T-cell killing of tumor cells, rather than as the checkpoint target. The second is the ecological resilience theory, according to which different microbial communities are considered more tolerant of perturbations and better able to maintain metabolite networks that protect mucosal health and support immune homeostasis. The third is precision host modulation. The microbiome is defined as an actionable drug-sensitivity layer and can, in theory, be manipulated by diet, bacterial consortia, probiotics, or fecal microbiota transplantation. [10-12,20,21]

Collectively, these views imply a causal mechanism rather than a basic biomarker paradigm. Microbiome adjustments can alter checkpoint outcomes by modulating community diversity, augmenting beneficial taxa, enhancing immune-active metabolites, depleting proinflammatory pathobionts, and indirectly by altering the tumor microenvironment via systemic immune programming. Figure 1 summarizes the conceptual pathway.[3-5]

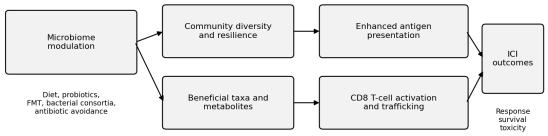

Figure 1: Conceptual pathway linking gut microbiome modulation to immune checkpoint inhibitor outcomes in solid tumors. Source: Adapted from recent clinical and mechanistic reviews.[3-5]

It is against this backdrop that the current paper conducts a secondary qualitative review to conceptualize how gut microbiome modulation has been conceptualized, the type(s) of modulation linked to benefit or harm, and the methodological characteristics that serve as strengths or weaknesses of the evidence base. The emphasis is no longer on a pooled meta-analysis of effect sizes, but rather on a thematic synthesis of mechanisms, outcomes, and appraisal issues within the clinical literature.

MATERIALS AND METHODS

In this paper, the structured secondary qualitative review design was adopted. Open and accessible sources (PubMed, Europe PMC, Crossref, and Google Scholar) were searched, and backward citation chasing of articles was performed to identify studies with clinical impact and more recent trials that met the specified search criteria and were published recently. Search terms were gut microbiome, microbiota, fecal microbiota transplantation, diet, probiotics, antibiotics, immune checkpoint inhibitors, anti-PD-1, anti-PD-L1, CTLA-4, melanoma, non-small cell lung cancer, renal cell carcinoma, hepatobiliary cancer, and solid tumors. The literature on microbiome and checkpoint blockade acceleration in humans dated between 2017 and April 2026 inclusive was included, as the clinical literature in this field began to pick up on the acceleration of the concept after the initial reports on the microbiome in human melanoma and the study in epithelial tumors.

Only human primary studies were eligible and had to provide a connection between gut microbiome composition or microbiome-modifying exposures and the clinical outcome of checkpoint inhibition in solid tumors. The findings synthesis did not cover reviews, animal-based studies, conference comments, or purely mechanistic laboratory papers, but the review literature was applied independently to the contextual framing. Fifteen primary studies were purposively selected because they were the main clinical traditions in the field, i.e., studies of baseline microbial signatures, disruption studies, studies examining antibiotics or other co-exposures, and active modulation studies using diet, bacterial products, or fecal microbiota transplantation. The information collected included data on the type of tumor, sample size, design, sequencing strategy, modulation strategy, outcome definition, primary findings, and methodological strengths and weaknesses. The interpretation was presented through an interpretive thematic procedure, in which studies were also coded according to the kind of modulation discussed and subsequently juxtaposed by the repetitive patterns of explanation.

RESULTS

A commonality in bacterial signatures across the fifteen main studies was not achieved, but three analytical themes were. On these themes, the most compelling data were observed in designs that related stool profiling to clinical endpoints and, when feasible,

to translational immune correlates. Simultaneously, almost all studies were threatened by small sample sizes, diet-based confounding, antibiotic exposure, geographic variation, and unstandardized microbiome pipelines. The evidence architecture of the included primary studies is presented in Figure 2, and Table 1 summarizes the thematic framework employed in the synthesis.

Table 1: Thematic framework and recurring appraisal issues across the 15 primary studies

Theme	Studies (n)	Typical outcome link	Recurring methodological strength	Recurring methodological limitation
Baseline ecological signatures	7	Diversity and responder-enriched taxa linked with better outcomes	Prospective translational profiling	Small cohorts; platform and geography effects
Disruption and co-exposures	4	Antibiotics and ecological instability are linked with weaker benefits	Clinically relevant exposure assessment	Confounding by indication; incomplete adjustment
Therapeutic engineering	4	FMT, diet, or bacterial products suggest modifiable response states	Interventional designs and immune correlates	Early phase; underpowered; heterogeneous donor or conditioning strategies

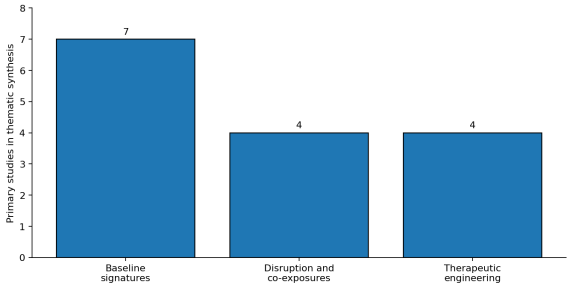

Figure 2: Evidence architecture of the 15 primary studies synthesized in the findings section. Source: Adapted from recent clinical reviews of microbiome-directed immunotherapy evidence.[12,22]

Baseline ecological signatures and response phenotypes

In baseline microbial architecture studies, phenotypes of responders and non-responders tended to indicate that they are ecologically different, but the specific organisms differed by population and platform. Frankel et al. and Chaput et al. provided early and useful work on melanoma, as their prospective, clinically anchored studies indicated that pretreatment microbial patterns were not only associated with checkpoint response but also with the risk of colitis.[23,24] They were strong in translational ambition, particularly in integrating metagenomic or metabolomic profiling with clinical outcomes. Still, their primary fault was scale, as both experiments were only small, individual disease experiments and thus susceptible to unreliable taxonomic results. Gopalakrishnan et al. and Matson et al. contributed to the area of research by examining anti-PD-1 aided melanoma and connecting enhanced commensals and higher alpha diversity with enhanced reaction.[25,26] Gopalakrishnan et al. provided more in-depth host immune characterization, and Matson et al. provided functional confirmation by fecal transfer experiments. Nevertheless, both were purely observational and focused on melanoma, which restricted their applicability to other solid tumors.

This theme was not limited to melanoma. Jin et al. found that increased diversity was correlated with positive anti-PD-1 response in Chinese patients with non-small cell lung cancer. Still, Zheng et al. and Mao et al. found dynamic microbial signatures correlated with response in hepatocellular and hepatobiliary cancers.[27-29] These articles are significant as they shifted the literature beyond a wanton spectacle of melanoma and implied that microbiome-response relationships are not limited to a single tumor manifestation. However, the cross-tumor analogy also revealed an issue of methodology. Taxa that seem good in one cohort are not necessarily recreated in the other. This can be due to actual biological dependence in

context, or it could be due to differences in sample dispensation, depth of sequencing, previous drug usage, and diets in different regions. The most robust aspects of the literature on the baseline signature are its demonstration of ecological patterns of diversity, resilience, and network structure. In contrast, the least robust are attempts to overinterpret single-organism observations as universal biomarkers.

Disruption, incidental modulation, and ecological fragility

One of the second themes concerned ecological interference and incidental modulation. All three articles demonstrated a negative relationship between antibiotic exposure around the initiation of a checkpoint and outcome in epithelial tumors or non-small cell lung cancer.[30-32.] Particularly influential was Routy et al., an integrative, multicenter clinical study with mechanistic validation implicating Akkermansia muciniphila. The fact that the field was shifted by that translational bridge, so that it moved from correlational to biological plausibility, is a strength. Derosa et al. extended external relevance by examining renal cell and lung cancer. Yet both were still unable to avoid confounding by indication, since patients who receive antibiotics tend to be sicker, more inflamed, or more complex. The negative signal was supported by Hakozaki et al. in a smaller retrospective cohort. Still, effect estimates are unstable, and adjustment for confounding factors is difficult in such a small cohort.

The literature on deliberate but low-intensity modulation was more mixed. Spencer et al. revealed that the higher the dietary fiber intake, the better progression-free survival in melanoma, and that the use of over-the-counter probiotics with reduced diversity and immune characteristics was less desirable.[33] The methodological aspect of this study was great as it combined diet, stool profiling, and immune analyses. Still, the dietary exposure involved was partially self-reported and thus susceptible to measurement error. Unlike the relatively consistent harm signal from antibiotics, the data supporting causal effects of probiotic supplementation were hard to interpret, as healthier behavior, co-medication trends, and choice of clinician were seldom disentangled. Taken together with other evidence, this theme indicates that, more consistently than simplistic supplementation can, the microbiome is susceptible to random interference. The moral of the comparison is that an ecological setup is more significant than merely adding bacteria.

Therapeutic microbiome engineering and proof of concept

The third theme was the therapeutic engineering of microbiomes, as it presented the strongest evidence that human checkpoint responsiveness can be transformed. The researchers Baruch et al. and Davar et al. utilized fecal microbiota transplantation in anti-PD-1 refractory melanoma and reported that a small group of previously inaccessible patients had new clinical responses following the use of stool from well-selected responders.[34,35] Causal ambition is the significant strength of these studies. They directly interfered with the microbiome, unlike observational cohorts, and observed downstream immunologic remodeling. They had significant limitations, though, as both were early phase, small, non-randomized, and limited to melanoma. There were also differences in donor selection, conditioning regimens, and the definition of response, which made it challenging to compare studies.

Further experiments perfected, but made the image even more complicated. Combining nivolumab plus ipilimumab in metastatic renal cell carcinoma with the live bacterial product CBM588.36, as Dizman et al. showed encouraging results, with an advantage over previous observational studies. Still, the sample size is too small, and a primary endpoint was added post-enrolment, so there is no certainty despite the encouraging signal. Routy et al. have demonstrated the feasibility of fecal microbiota transplantation with anti-PD-1 therapy from healthy donors in advanced melanoma, including activation of the immune response, opening the intervention space beyond respondent donor stool alone. In contrast, Glitza et al. have provided a valuable corrective bias lesson in a placebo-controlled trial of microbiome modulations in melanoma.[37,38] The latter study is methodologically better than much of the previous literature, but the interference of low accrual and the immunologic implications of antibiotic preconditioning limited the interpretation of efficacy. The theme of the trials is that engineered modulation is viable and biologically active, but it also demonstrates why the discipline has not yet become a standard practice. Whether or not microbiome manipulation can alter immunity is no longer the key question. It is the way to do it in a reproducible, safe, and tumor and host-specific fashion.

DISCUSSION

The synthesis proposes that gut microbiome regulation is involved in the effects of immune checkpoint inhibitors, following an ecological, rather than a single-organism, model. This interpretation is

consistent with emerging reviews that characterize the microbiome as a systems-level controller of checkpoint efficacy, toxicity, and resistance, rather than as a list of useful taxa.[3-9,16-22] To consider the studies included within the framework of the cancer immunity cycle, it can be suggested that positive communities can help promote antigen presentation, the recruitment of effector T-cells, and inflammatory set points conducive to checkpoint reinvigoration. Applied to ecological resilience theory, they also provide answers to the observation that diversity frequently predicts benefits beyond those of an individual bacterium, and to why antibiotics can have disproportionately harmful effects.[10-12,20,21] This sense indicates that the field has shifted its paradigm from a taxonomy-focused to a function-focused paradigm.

The results also highlight the distinction between passive association and actionable modulation. Clinical and translational review articles increasingly conclude that microbiome-directed therapy has potential; however, it relies on donor selection, underlying dysbiosis, conditioning, metabolite activity, diet, and tumor biology, rather than on generic supplementation. [12, 15, 18, 19, 22.] That view is in line with the current analysis. The field received its first alert from observational studies, which are extremely susceptible to confounding by diet, comorbidity, corticosteroid exposure, proton pump inhibitors, and frailty in the clinical setting. The seeming regularity of the harm caused by antibiotics is thus more persuasive than the initial data on business probiotics. In comparison, the trials of fecal microbiota transplantation and live bacterial products indicate that causal intervention can be used, but also demonstrate that efficacy is not universal and depends on the circumstances.

Another implication is regarding theory. Whereas precision oncology has long focused on tumor intrinsic markers, a broader host ecology framework is currently being synthesized, in which microbial diversity, metabolite interactions, and mucosal barrier activity are now included in treatment sensitivity. Such a theoretical 180-degree shift helps explain why two patients with ostensibly comparable tumor biomarkers can differ markedly in their response to the same checkpoint regimen. It further indicates that future trials ought to stratify not only by tumor histology and PD-L1 status, but also by microbiome status, recent antibiotic use, diet quality, and metabolic phenomenology.[1,2,5,13,14,21]

The review has some limitations. It is interpretive and not meta-analytic, and the current evidence base is weighted toward melanoma, with less strong interventional data in lung, kidney, hepatobiliary, and other solid tumors. Methods of study were heterogenous and a few of the recent interventions are either in the early phase or underpowered. However, when causal routes, ecological context, and methodological design are equally significant as pooled effect sizes, then the thematic methodology is appropriate. Overall, the evidence warrants larger randomized studies with standardized sampling, more rigorous dietary control, harmonized sequencing, and function-focused endpoints. In the meantime, the gut microbiome can be considered a host biomarker warranting serious consideration and an experimental partner in checkpoint oncology therapy.[12,21,22]

CONCLUSION

The evidence presented in this manuscript shows that the gut microbiome is a key host factor in the efficacy of immune checkpoint inhibitors in solid tumors. The recurring patterns across the studies were that favorable response was more often associated with high microbial diversity and enrichment of informatogens such as Akkermansia, Faecalibacterium, Bifidobacterium, and taxa of the Ruminococcaceae family, and antibiotic-induced dysbiosis was often related to poor treatment response. These data substantiate the assumption that checkpoint inhibitor success depends not only on tumor intrinsic biomarkers but also on systemic immune control achieved by the intestinal ecosystem.

Meanwhile, the review indicates that the field remains methodologically heterogeneous. The differences in tumor type, sequencing platform, sampling methodology, nutritional exposure, history of medications, and response definition complicate straightforward comparison and limit the implementation of common microbial signatures. Transplantation of fecal microbiota, dietary manipulation, and live biotherapeutic products, based on interventional studies, provide promising evidence of concept but have not been tested enough to be adopted in clinical practice.

Altogether, the concept of gut microbiome modulation is an effective option for enhancing immunotherapy outcomes, but its clinical application requires more rigorous, controlled, and systematic trials. Next-generation practice in oncology research and treatment might involve applying microbiome profiling to specific microbiomes and using these profiles to inform precision immunotherapy.

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