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Gut Microbiome Control of Tumor Immune Checkpoint Inhibitor Response: Mechanistic Insights and Clinical Translation

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Abstract. Here, we summarize available data on mechanisms by which the gut microbiota may affect immune checkpoint inhibitors (ICIs) and discuss potential therapeutic approaches targeting the microbiota. Gut microbiota could affect both antitumor immunity and immune-related toxicities through orchestration of the mucosal and systemic immune response, altering the abundance of functionally relevant taxa, changing community diversity, producing immunomodulatory metabolites, which leads to immunomodulation, inducing innate immunity, modulating adaptive immunity by activation of pattern-recognition pathways, as well as affecting organ crosstalk such as the gut-lung axis, etc. Based on studies of Akkermansia, Bacteroides, short-chain fatty acids, inosine, tryptophan metabolites, or fecal microbiota transplantation, it seems possible that modulating the microbiome could improve response rates to ICI therapy, reduce off-target toxicity, and enable more individualized cancer immunotherapy.

Keywords: gut microbiome, immune checkpoint inhibitors, tumor immunity, microbial metabolites, fecal microbiota transplantation

1. Introduction

Immune checkpoint inhibitors (ICIs) have reshaped the management of many solid tumors, yet their benefits remain uneven across patients. Even where PD-1/PD-L1 and CTLA-4 blockade have become standard treatments, only a subset of patients achieve durable responses, and acquired resistance after an initial response continues to limit long-term survival [1]. Early explanations for ICI failure emphasized tumor-intrinsic mechanisms, including impaired interferon-gamma (IFN-gamma) signaling, loss or reduction of antigen-presentation machinery such as HLA, TAP1, and TAP2, compensatory expression of checkpoints including TIM-3 and LAG-3, and activation of oncogenic pathways such as Wnt/beta-catenin and PI3K/AKT [2, 3]. The tumour milieu also plays a role, by inducing growth and metabolic reprogramming of MDSCs, which support immune escape. But such tumor-based models do not completely explain the wide interindividual variation of ICI efficacy. Increasing evidence now implicates the gut microbiome as an immune-regulating organ-like system capable of influencing checkpoint blockade response and resistance. Beneficial microbes such as Bifidobacterium or Akkermansia muciniphila might boost dendritic-cell activity and

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enhance the infiltration of CD8+ T cells into tumours, whereas microbial products such as short-chain fatty acids and tryptophan metabolites can tune T-cell metabolism, differentiation, and effector function via receptor-mediated and metabolic pathways [3-5]. Therefore, clarifying how the gut microbiota interacts with host immunity

and the tumour microenvironment will be important to understand ICI resistance and design rational microbiome-based combinatorial therapies [1-5].

2. Immunological basis for microbiome-mediated effects on ICI response

The intestine serves as a significant immune interface instead of merely a passive digestive surface. The mucosal immune system interacts intimately with systemic immunity, enabling signals produced in the gastrointestinal tract to affect remote tissues. Intestinal epithelial cells serve as a physical barrier and function as immune sentinels: they identify microbial products via pattern-recognition receptors and secrete cytokines that facilitate immune cell recruitment and activation. The epithelial compartment contains abundant intraepithelial lymphocytes, including alphabeta and gammadelta T-cell populations, which respond rapidly to epithelial injury or infection. In addition, M cells transport luminal microbial antigens across the epithelial layer to the lamina propria, where dendritic cells can initiate adaptive immune responses. In this way, the gut epithelium functions as a key gateway between microbial communities and systemic immune regulation [1-5].

The lamina propria hosts a dense and diverse immune-cell network consisting of dendritic cells, macrophages, T cells, B cells, and natural killer-like cells (NKC) and innate lymphoid cells (ILCs). DCs uptake antigens and travel to MLNs to assist in the activation of naïve T cells. Macrophages are involved in pathogen clearance and fine-tuning of inflammation.T and B cells sustain mucosal immune homeostasis via cellular immunity and antibodies, respectively, whereas secretory IgA from intestinal B cells limits pathogen adhesion and facilitates the maintenance of microbiome homeostasis [1-5].

Immune activity initiated in the gut can extend beyond the intestinal mucosa. T cells and B cells intestinal sites may travel through mesenteric lymph nodes into the circulation and subsequently home to peripheral organs or other mucosal tissues. At the same time, microbial metabolites can enter the bloodstream and act at distant sites. Through these routes, the intestinal microbiota is able to influence systemic immune tone and may thereby affect the therapeutic performance of cancer immunotherapy [1-5].

The overall clinical and preclinical data support the association between the composition of the gut microbiota and the effectiveness of immune checkpoint inhibitor treatment, where Akkermansia muciniphila has emerged as one of the taxa most frequently reported for favorable response. Metagenomic studies performed on patients treated with PD-1/PD-L1 blockade revealed a consistent increase in intestinal abundance of A.muciniphila in responders compared with non-responders for various cancers like non-small cell lung cancer, renal cell carcinoma, and melanoma [6-8]. Animal model evidence supports such an association, since transfer of responsive donor faecal microbiota in GF or antibiotic-treated animals may restore ICI response, and the incorporation of Akk can partially reverse antibiotic resistance [9-10]. Mechanistically, Akk could augment CBP via multiple arms of immunity, including induction of IL-12dependent Th1 responses, promotion of T-cell traffic into tumours, and elevated secretion of cytokines including IFN-gamma and IL-2. Akk-associated signals may also stimulate pathways such as JAK-STAT and STING, facilitating dendritic-cell maturation and T-cell activation [11-13]. Additionally, it may affect the tumour immune microenvironment indirectly via altering host metabolism, such as those related to bile acids and lipids [14].

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The evidence for Bacteroides is less robust than that for Akkermansia. Bacteroides species are common anaerobic bacteria present within the human gut, which modulate immune function through their ability to digest complex polysaccharides and produce metabolites including short-chain fatty acids; some studies have suggested that B. fragilis or B. thetaiotaomicron can augment response to anti-CTLA-4 via promotion of a Th1 response [15-16]. Other reports have associated a higher abundance of Bacteroides with lower response to ICIs or shorter PFS [17, 18]; however, these different findings could be due to differences in the tumour categorization, host features, treatment setting, and strain-dependent functional distinctions within the genus [15-18].

Besides individual bacterial taxa, microbiome features on a community level appear important in immunotherapy. Alpha diversity, which represents the diversity and abundance of species in a sample, is often used for describing the general ecology profile of the intestinal microbiota [19].

Higher alpha diversity has been associated with a stronger microbiome overall, which can boost antitumor immunity through an increased repertoire of immune-stimulatory molecules/metabolites available to the host. A number of clinical cohorts reported higher gut microbial diversity in ICI responders, with favorable associations with progression-free or overall survival. However, there are limitations to the use of alpha-diversity as a biomarker. Some studies failed to find any significant differences between responder and non-responder groups, indicating that diversity alone is insufficient to capture the functional immunological impacts of the microbiota [20-27].

As such, the effect of the microbiome on ICI response is best viewed as multivariate in nature, and accurate prediction likely requires an examination across all microbes,strain-specific traits, functional gene sets, metabolome profiles, or even host immunity conditions rather than using one single ecophysiological parameter [22-27].

3. Principal mechanisms linking gut microbes to immunotherapy response

3.1. Microbial metabolites and T-cell regulation

The microbial metabolite provides a biochemical pathway by which intestinal microbes can communicate with host immunity. Short-chain fatty acids (SCFAs), inosine, and tryptophan-derived metabolites strongly correlate with T-cell activity and ICI response. Epigenetically modulate T-cell fate determination, effector function, memory formation, metabolism, receptor signaling, and changes in cell metabolism, which eventually influence antitumor immunity [25].

SCFAs are mainly derived from fermentation by intestinal microflora of dietary fibers to produce acetate, propionate, and butyrate that serve as an energy source for intestinal epithelial cells and regulate immunity through inhibiting HDACs and activating G-protein coupled receptors (e.g., GPR41 and GPR43). For example, butyrate may increase histone acetylation; promote Foxp3 expression; induce regulatory T-cell differentiation; and, under certain conditions, promote IFNgamma/granzyme B expression on CD8+ T cells to enhance cytotoxic function. SCFAs may also promote generation of memory T-cells through regulation of mTOR and oxidative phosphorylation pathways. Taken together, all these effects can provide reasonable explanations why SCFAs might improve ICI's antitumor efficacy [28].

Inosine is another microbiota-derived metabolite, produced by organisms such as Bifidobacterium. By engaging the adenosine A2A receptor, inosine can trigger downstream

cAMP-PKA signaling and alter T-cell metabolism and function. Prior studies indicate that, in appropriate immune-stimulatory settings, inosine promotes Th1/Tc1 polarization and augments antitumor immunity. It may also interact with mTOR, NF-kappaB, and energy-metabolism pathways. Because adenosine-A2A signaling is often immunosuppressive within tumors, however,

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the immunological consequences of inosine are likely context-dependent and require further clarification [29, 30].

Tryptophan metabolism is another connection of the microbe with immune control. Tryptophan can be converted by host and microbial enzymes to kynurenine, as well as various indoles, many of which communicate via the aryl hydrocarbon receptor (AhR). Indoles produced by microbes such as indole-3-carbaldehyde and indole-3-acetic acid can modulate T-cell differentiation and cytokine production through the AhR pathway. On the other hand, IDO-mediated kynurenine synthesis in the tumoral environment prevents T-cell proliferation and stimulates regulatory T-cell differentiation, facilitating immune evasion. Manipulating tryptophan metabolism and/or the microbiota that produce these metabolites may improve response to immune checkpoint inhibition [31].

3.2. PRR signaling and dendritic-cell maturation

Microbial constituents may directly affect antitumor immunity via innate immune detection. Pattern-recognition receptors (PRRs), especially Toll-like receptors (TLRs) and NOD-like receptors (NLRs), play a pivotal role in the maturation of dendritic cells and the presentation of antigens [32, 33].

TLRs reside at the plasma membrane or in endosomal compartments and recognize conserved microbial motifs. TLR4 recognizes lipopolysaccharides of Gram-negative bacteria, TLR2 recognizes peptidoglycan and lipoteichoic acid; TLR5 recognizes bacterial flagellin. Binding of ligands activates either MyD88- or TRIF-dependent pathways, leading to NF-kappaB and MAPK activation, production of inflammatory mediators as well as increased expression of costimulatory molecules. The mature DCs then upregulate their expression levels for CD80, CD86, and MHC molecules as well as secrete cytokines such as IL-12, thus enhancing T-cell stimulation and the antitumoral immune response. In turn, NLRs analyze intracellular components of bacteria. NOD1 and NOD2 detect peptidoglycan fragments and activate the RIP2-NF-kappaB pathway, thus increasing the expression of pro-inflammatory cytokines as well as dendritic cell maturation. NOD2 is capable of stimulating autophagy and improving antigen processing and presentation. The collaboration between TLR and NOD pathways can enhance IL-12 synthesis in dendritic cells and bolster Th1-type immunity [32, 33].

During homeostasis, continuous but limited stimulation of PRRs by the microbiota contributes to maintaining immunity while preventing inflammatory responses. For oncology, appropriately regulated PRR activation would also likely be beneficial since this promotes antigen presentation and T-cell activation, which may enhance the effectiveness of checkpoint blockade [34].

4. Gut microbiota in ICI-related toxicity

Although ICIs could markedly improve outcomes for a variety of cancers, they might cause immune-related adverse events (irAEs). The toxicities could involve multiple organs, with the gastrointestinal system and lungs as the organs most commonly involved, causing immune-mediated colitis and immune-related pneumonitis, respectively; recent research suggests dysbiosis affects the onset and severity of such events. The gut-lung axis offers an attractive paradigm to understand such a link: both the intestine and lung are mucosal immune organs and communicate through immune-cell trafficking, circulating metabolites, and neuroendocrine pathways. Gut-derived metabolites such as SCFAs may be circulated to the lung, where they modulate local immunity, while lung inflammation/infection may alter gut microbiota composition. This bidirectional control implies that dysbiosis may promote intestinal inflammation, but also inflammatory susceptibility at distant

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organs. Different mechanisms can connect the gut microbiota with immune-mediated colitis and pneumonitis [16, 17].

Several potential mechanisms could relate the gut microbiome with immune-mediated colitis and pneumonitis: First, intestinal microbes may influence distant organs through modulation of systemic immunity; evidence from germ-free animal studies suggests absence of gut microbes impairs lung immunomaturity, making them susceptible to lung infection. Second, microbial metabolites mediate cross-organ immunoregulation. SCFAs regulate macrophage and dendritic cell function through G-protein-coupled receptors and by inhibiting histone deacetylase, thus limiting pathological inflammation. Upon antibiotic treatment and infection, which disturb microbiota composition, reduced levels of SCFAs might be involved in deregulation of inflammasomes such as NLRP3, promote IL-1β and IL-18 release, and increase inflammation. Thirdly, dysbiosis can potentially modulate Th17/Treg homeostasis. The Th17 cells aggravate co litis a n d pneumonitis, while the Tregs suppress immune activation and tolerance. The absence of butyrate-producing bacteria may impair Treg differentiation, thus augmenting inflammation not only at the GI level but also in the lung. Finally, microbiota maintains the mucosal barrier through increased mucus production and TJ expression. Breakdown of the barrier allows bacteria component such as LPS into the bloodstream, which activate the TLR4/NF-kappaB pathway and induce further inflammatory responses in the body, enteritis, or pneumonitis [16-18, 28, 32].

These mechanisms allow microbiome manipulation as a means of reducing ICI toxicity. Probiotics such as Faecalibacterium prausnitzii and Bacteroides fragilis can promote the differentiation of Tregs and reduce inflammation, which may be utilized for the treatment of immune-mediated colitis (e.g., fecal microbiota transplant and/or probiotics). These two modalities are both promising treatments for ICI-associated colitis, with several case reports supporting their use. Metabolites provide an additional layer of treatment: SCFAs have the potential to inhibit NF-kappaB signalling, regulate dendritic cells, and immune homeostasis; the tryptophan derivatives act through AhR to modulate innate lymphoid cells; and the secondary bile acids participate in inflammation control through FXR and TGR5 receptors [35-39].

Collectively, the gut microbiota influence irAEs such as immune-mediated colitis and pneumonitis via their impact on immune cell differentiation, the availability of metabolites, and the integrity of the mucosal barrier. Better understanding of microbiota-immune interactions might reveal biomarkers for risk assessment and therapeutic targets to prevent/treat ICI-related toxicity [16-18, 35-39].

5. Microbiome modulation as a translational strategy: clinical use of FMT

Since gut microbes play a critical role in irAE pathogenesis, therapeutic re-shaping of the microbiota is now an enticing strategy to treat and possibly prevent such complications. Fecal microbiota transplant (FMT), among the various possible treatments, is receiving special interest since it consists of transferring an entire healthy microbial ecosystem instead of one single microorganism. This broad ecological replacement could prove particularly useful in refractory irAEs that remain despite conventional immunosuppressive therapy [35-38].

Efficacy and safety of FMT for refractory immune-related colitis

Refractory immune-related colitis in patients unresponsive to glucocorticoids, infliximab and/or other standard therapy leaves few treatment choices for clinicians, and chronic inflammation may be severe or even fatal. Here, FMT was explored for rescue therapy and is gaining increasing support by case reports and limited cohorts [35-38].

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Clinical effectiveness: Generally, in case reports/small series, FMT was associated with marked improvement of refractory immune-mediated colitis. In the landmark report, Wang et al. (2018) reported on 2 patients with severe colitis, refractory to corticosteroid therapy and infliximab; after one/two FMT sessions, diarrhea/hematochezia rapidly disappeared with complete clinical response [35]. Further analyses reported similar outcomes, including successful management of an acutely unwell patient with severe GI bleed secondary to ICI-related colitis [36]. A systematic review indicates that FMT may help to improve symptoms and assist in the recovery of microbiota, although it is limited by small sample size, as well as nonrandomized methods [36-38].

Mechanism of action: There is convincing immunological reprogramming behind the positive effect of FMT for immune-systemic colitis after effective transfer; the local inflammatory environment within the gut mucosa shifts toward an anti-inflammatory state, with studies showing decreased numbers of pro-inflammatory CD8+ T cells and increased numbers/ratios of CD4+FoxP3+ regulatory T cells [38]. Such changes suggest that the donor microbiota can reestablish regional immune homeostasis, reducing ongoing autoimmunelike injury to the intestinal mucosa; the transition from an inflammatory towards a tolerogenic mucosal milieu likely facilitates long-term control over colitis.

Safety and tolerability: Clinical reports indicate that FMT is generally well tolerated with immune-colitis [37]. Adverse effects are generally mild and transient, such as transient bloating, belching, abdominal pain, or low-grade pyrexia. Transient rises in inflammation markers, such as CRP or IL-6, have been observed in some patients after FMT, sometimes with fever. It is possible that these findings suggest early immune response of the donor microbes to the host body, usually resolving in hours to days with no lasting sequelae [39]. However, FMT carries serious risks, especially about transmissible infections such as unknown viruses or multidrug-resistant bacteria. Rigorous screening of donors and standardized production methods can therefore contribute significantly to safety.

Longevity, repetition, and existing evidence deficiencies

Although FMT could rapidly treat refractory immune-mediated colitis, the long-term effect remains controversial. Longterm follow-up data, particularly beyond one year, are limited in ICI related colitis, and most data are derived from case reports, small cohorts, i.e., short observation periods. To cautiously infer possible longitudinal patterns, we can consider data on UC and recurrent C. difficile infection; but these diseases are not equivalent with immune-related colitis since they have different pathophysiologic mechanisms and immune mediators [40-44].

UC Evidence: UC is a chronic inflammatory bowel disease that shares some of the immunology associated with immune-mediated colitis. In moderate-to-severe UC, remission following single or short-course FMT is not usually sustained for very long; one study showed that the 52week relapse rate was as high as 54.5% amongst those who had been successfully treated with FMT to induce remission [40]; another, longer term follow up study from corticosteroid dependent UC saw 76.9% of patients experience a first relapse at a mean follow up of 14 weeks.8 months [41]. These results indicate that once chronic immune dysregulation is in place, a single time-point microbial reboot might slowly fade away with the host milieu driving the microbiota back towards a pathogenic configuration. Maintenance FMT may thus need to be given periodically following the induction of remission, to avoid a high relapse rate in some patients [42].

CDI evidence: FMT is very effective in recurrent C. difficile infection, and the majority of studies report a rather low rate of long-term recurrences ranging around 0%-18% [43, 44]. The pathophysiology in CDI is fairly straightforward: antibiotic-associated dysbiosis allows for overgrowth by one pathogen, C. difficile. FMT may restore ecological competition and microbiome

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function, thereby removing the niche for the pathogen to thrive in. The case for immune-mediated colitis is more complicated, as this takes place in an animal that had its immune system turned on by checkpoint inhibition, and while microbe levels are restored, the aberrant immune milieu can persist. Thus, it is plausible that the probability for a recurrent immune-mediated colitis after FMT will be somewhere in between the negligible rate of relapse observed during CDI and the higher incidence of relapse encountered by patients with UC.

Limitations and pitfalls: Several limitations exist with respect to application of FMT in immune-mediated colitis. In general, the quality of evidence is still low, as much data come from observational studies, case series and/or non-randomised clinical trials rather than RCTs. In addition, there is no standard protocol for FMT. Donor inclusion/exclusion criteria, faecal processing techniques, administration route, dose, and frequency of therapy vary between studies, complicating direct comparison. FMT is an inherently complex biological therapy since what is actually being transplanted is essentially a large, poorly defined mixture of microbes, metabolites, and microbes.

Limitations and challenges: There are some barriers to using FMT for immune-related colitis. Evidence is generally weak, as most of the data are based on retrospective analyses and/or case reports/small uncontrolled studies instead of randomised controlled trials. Also, FMT protocols are non-standardized. Donor eligibility, stool preparation, delivery route, dose, and treatment frequency vary amongst the studies, making a direct comparison difficult.FMT is also an inherently complicated biological intervention: the transplanted matter contains a large, ill-defined mixture of microbes, metabolites, and microbial byproducts. Long-term safety, including effects on the development of metabolic syndrome or carcinogenesis, requires constant vigilance [35-39].

To sum up: FMT offers an optimistic salvage therapy option for the treatment of refractory immune-mediated colitis with encouraging short-term efficacy as well as an acceptable safety profile based on reported studies; however, whether it will be durable, whether it can recur if needed, when it might occur, and how best to preserve it. Rigorously designed, multicenter, prospective study of longer duration in order to better understand the patient population who will benefit most, and how to best administer FMT, and whether a maintenance transplant will be needed or possible [35-44].

6. Conclusions and future perspectives

The potential that the gut microbiota have in modifying anti-tumour immunity is huge, yet difficult to translate to everyday clinical use due to large variations between individuals or standardised methods of collection, sequencing, and bioinformatic analysis, which limits reproducibility between studies. Therapeutics aiming at specific metabolites such as SCFAs or inosine require further substantiation given the complexity of bioavailability,dose-effect relationships, and signal feedback loops. In order to overcome the limitations, future studies should develop a multicenter long-term cohort study and combine AI technology with multi-omics approaches for uncovering microbiota-host-immune crosstalk. Finally, developing international standardised technical guidelines will also be important. In the long-term, microbiome-informed oncology could become a precision paradigm whereby microbiota signatures inform individualised ICI regimens, personalized FMT, individualised prebiotic use and diet modification [1-5, 25, 35-44].

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