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# Gut microbiota influences the efficiency of immune checkpoint inhibitors by modulating the immune system (Review)

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**Abstract.** Immune checkpoint inhibitors (ICIs) are commonly utilized in tumor treatment. However, they still have limitations, including insufficient effectiveness and unavoidable adverse events. It has been demonstrated that gut microbiota can influence the effectiveness of ICIs, although the precise mechanism remains unclear. Gut microbiota plays a crucial role in the formation and development of the immune system. Gut microbiota and their associated metabolites play a regulatory role in immune balance. Tumor occurrence and development are linked to their ability to evade recognition and destruction by the immune system. The purpose of ICIs treatment is to reinitiate the immune system's elimination of tumor cells. Thus, the immune system acts as a communication bridge between gut microbiota and ICIs. Varied composition and characteristics of gut microbiota result in diverse outcomes in ICIs treatment. Certain gut microbiota-related metabolites also influence the therapeutic efficacy of ICIs to some extent. The administration of antibiotics before or during ICIs treatment can diminish treatment effectiveness. The utilization of probiotics and fecal transplantation can partially alter the outcome of ICIs treatment. The present review synthesized previous studies to examine the association between gut microbiota and ICIs, elucidated the role of gut microbiota and its associated factors in ICIs treatment, and offered direction for future research.

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## 1. Introduction

Immunotherapy has emerged as a rapidly advancing treatment for tumors in recent years. Immunotherapy is based on the tumor immune escape mechanism, which manipulates the immune system to reactivate the antitumor immune response and overcome the pathways that lead to tumor escape (1). Current immunotherapy methods encompass immune checkpoint inhibitors (ICIs), adoptive cell therapy, oncolytic viruses and cancer vaccines. Among them, ICIs, including antibodies against programmed cell death protein 1 (PD-1), its ligand PD-L1, cytotoxic T lymphocyte antigen-4 (CTLA-4), lymphocyte activation gene 3 (LAG3), T cell immunoglobulin and mucin domain 3 (TIM3), and indoleamine 2, 3-dioxygenase 1 (IDO), have been widely and rapidly developed in clinical practice, achieving satisfactory results (2). However, there are still several shortcomings in the treatment with ICIs. Only a small number of tumor patients respond to ICIs, and there is still the possibility of drug resistance. Moreover, it is unable to address the disease progression and life-threatening nature for most cancer patients. Additionally, ICIs rely on the activation of autoimmune function to eliminate tumors, and these mechanisms may affect the self-tolerance of healthy tissues, leading to immune side effects known as immune-related adverse events (irAEs) (3). Gut microbiota plays a significant role in the physiological and pathological processes of the human organism. As a current research hotspot, it has made substantial progress in various fields. The potential connection between gut microbiota and ICIs has been extensively investigated in recent years, encompassing the relationship between gut microbiota and its associated metabolites, the clinical efficacy of ICIs, the correlation between gut microbiota and adverse events related to ICIs, the impact of antibiotic application on ICIs, and the application and effectiveness of probiotics and fecal transplantation in clinical practice (4). While the specific mechanism by which gut microbiota influences the treatment of ICIs remains unclear, the current research indicates that gut microbiota may serve as a crucial target for regulating the efficacy of ICIs, making its practical application in clinical settings highly promising (5). The present review

examined the relationship between gut microbiota and ICIs, provided a summary of the current research progress, and explored the potential interaction mechanisms and future prospects between these factors.

## 2. Gut microbiota and the immune system

*Gut microbiota*. The gut microbiota is a vast microecosystem that includes bacteria, archaea, fungi and viruses. Each person carries up to $10^{14}$ microbial species, ~99% of which are bacteria. The primary species are *Firmicutes* and *Bacteroidetes*, followed by *Actinobacteria* and *Verrucomicrobiota* (6,7). The gut microbiota is closely linked to the activities of life and plays a crucial role in numerous metabolic processes. For instance, the microbiota in the colon encodes a plethora of carbohydrate-active enzymes, allowing them to break down non-digestible dietary residues and release short-chain fatty acids. These microbes assist in the synthesis of micronutrients such as vitamin K, vitamin B12, biotin, folic acid and pantothenic acid, in addition to aiding in the absorption of calcium, magnesium and iron. The gut microbiota can also regulate intestinal endocrine function, nerve signals, bone mineral density, provide biogenic energy, synthesize neurotransmitters, and metabolize bile. Furthermore, the gut microbiota plays a crucial role in the maturation and sustained expression of the host immune response (8,9).

*Gut microbiota and the development of the immune system*. The influence of gut microbiota on the immune system begins during early life. The immune system develops in a relatively sterile fetal environment during early life, with its primary exposure to antigens derived from the newly established microbial community on the mucosal surface of the newborn. Exposure to microbes during early life can result in lifelong changes in the immune system (10). The infant receives natural passive immunity from the mother through the placental route during pregnancy. The maternal gut microbiota profile can influence the composition of immune cells in infants. The enrichment of *Dialister*, *Escherichia* and *Ruminococcus* in the maternal gut microbiota is associated with a lower proportion of granulocytes and a higher proportion of central naïve $CD4^+$ T cells ($CD4^+/CD45RA^+/CD31^-$) and naïve regulatory T cells (Treg) ($CD4^+/CD45RA^+$/FoxP3low) in cord blood (11). Maternal dietary habits and breastfeeding after birth can also impact the regulation of immune factors in infants (12,13). The gut microbiome undergoes significant changes before the age of 2.5 years under the influence of various factors, but it gradually stabilizes afterward and remains relatively constant throughout the lifetime of an individual (14). Different age groups exhibit distinct gut microbiota profiles, with *Bifidobacterium* being more prevalent in infants and children, while *Megamosna* and *Peptoniphilus* are relatively enriched in the elderly (15). For instance, *Akkermansia* is more abundant in the gut microbiota of frail elderly individuals. It is positively correlated with the elevation of interleukin 6 and can elevate serum inflammatory factor levels, as well as increase intestinal permeability (16). In conclusion, the influence of gut microbiota on the immune system plays a crucial role in life development and may affect both physiological and pathological processes.

*Gut microbiota influence the immune balance*. Increasing evidence suggests that gut microbiota can regulate the proliferation and expression of immune cells, particularly the balance between T helper cell 17 (Th17) and Treg cells (17). Th17 cells contribute to autoimmunity and inflammation, while Treg cells inhibit immune responses and maintain immune homeostasis. Both cell types initially differentiate from naive CD4 T cells under the influence of tumor growth factor (TGF)-β (18). A previous study demonstrated that the balance between Th17 and Treg cells in the lamina propria of the mouse small intestine is influenced by the presence of *Cytophaga-Flavobacter-Bacteroidetes* bacteria. Specifically, Th17 cell differentiation is associated with the presence of these bacteria, while germ-free mice exhibit an increase in Treg cells in the lamina propria (19). Furthermore, a previous study has demonstrated that the presence of mixed *Clostridium* in mice leads to an upregulation of Treg cell abundance and function in the colon. This effect is attributed to the creation of a transforming growth factor-β enriched environment (20). Thus, it is plausible that Th17/Treg cells are regulated and proliferated by various species of gut microbiota. Research has demonstrated that *Bacteroides fragilis* (*B. fragilis*) can stimulate the proliferation of Treg cells through Toll-like receptor 2 (TLR2), consequently suppressing the activity of Th17 cells. As for the mechanism of action, a symbiotic factor known as polysaccharide A (PSA) produced by *B. fragilis* has been identified as a key player. PSA, a representative immunomodulatory molecule of symbiotic nature, can activate CREB-dependent transcription of anti-inflammatory genes through the coordinated activation of TLR2 and Dectin-1. This activation leads to the production of the immunomodulatory cytokine IL-10 by $CD4^+$ Treg cells. Consequently, immune tolerance is achieved, and it may serve as a mechanism for intestinal commensal bacteria to evade the immune system (21,22). In conclusion, gut microbiota plays a significant role in regulating the balance between proinflammatory responses and immune regulation, despite the precise underlying mechanisms remaining unclear.

*Gut microbiota-associated metabolites affect the immune system*. Increasing evidence supports the role of gut microbiota-derived metabolites in immune system regulation. The majority of metabolites associated with gut microbiota have been found to be involved in immune regulation, attenuating immune responses, and potentially contributing to immune tolerance. Extensive research on short-chain fatty acids (SCFAs), a well-studied group of metabolites, has demonstrated that SCFAs derived from mouse gut microbiota can activate STAT3 and mTOR in Th1 cells, upregulate the transcription factor B lymphocyte-induced maturation protein 1 (Blimp-1), and stimulate the production of IL-10 to preserve intestinal homeostasis (23). Butyrate, a metabolite produced by *Firmicutes* and *Fusobacteria*, can activate the expression of TGFB1 in human intestinal epithelial cells through the transcription factor SP1. This activation leads to the accumulation of Treg cells in the intestine, contributing to its immunomodulatory role (24). Following the consumption of propionic acid by patients with multiple sclerosis, there is a significant and sustained increase in Treg cells. Additionally, the mitochondrial function and morphology of Treg cells normalize, whereas the levels of Th1 and Th17 cells markedly decrease, indicating

the immunomodulatory effects (25). Metabolites associated with the microbiota, including taurine, histamine, spermine and bile acids, contribute to the maintenance of intestinal homeostasis through the regulation of NLRP6/NLRP3 inflammasomes (26,27). Probiotics such as *Lactobacillus rhamnosus* GG and factors derived from LGG broth culture supernatant can activate Akt, alleviate TNF-induced colonic epithelial injury, suppress cytokine-induced epithelial cell apoptosis, and foster intestinal epithelial homeostasis. Furthermore, LGG cell-free supernatant (LGG-SN) has been observed to enhance the sensitivity of human tumor cells to 5-fluorouracil and irinotecan (28,29). The outer membrane protein Amuc_1100 derived from *Akkermansia muciniphil* stimulates the production of IL-10 by activating TLR2 and TLR4 (30). The human gut Actinobacterium *Eggerthella lenta* disrupts the inhibition of the Th17 transcription factor Rorγt by cardiac glycoside reductase 2 enzyme, leading to Th17 activation in the intestine and the initiation of autoimmunity (31). Overall, certain metabolites associated with gut microbiota contribute to the maintenance of intestinal immune balance, safeguarding the survival of gut microbiota and protecting the intestinal tract from immune-related harm. Consequently, the intricate mechanism through which gut microbiota regulate the immune system via their metabolites necessitates further investigation.

## 3. ICIs therapy for cancer

Tumor immunotherapy is initiated by the mechanisms through which tumor cells evade the human immune system. Typically, the immune system can identify and eliminate tumor cells in healthy tissues based on tumor-associated antigens. Tumors, however, employ various immune processes to evade the immune system, including targeted modulation of Tregs function or secretion, antigen presentation processes, modification of immunosuppressive mediator production, development of immune tolerance, and evasion of immune system-mediated killing (32). Immune checkpoints play a crucial role in regulating the host's antitumor immunity. Currently, extensively studied immune checkpoints include PD-1, PD-L1, CTLA-4, LAG3, TIM3 and IDO. ICIs based on these targets have significantly enhanced the efficacy of tumor treatment and made substantial progress in recent years (33). PD-1, a receptor in the (immunoglobulin) Ig superfamily, negatively regulates T-cell antigen receptor signaling through its interaction with the specific ligand PD-L1. PD-L1, also referred to as B7-H1 or CD274, is expressed in numerous tumors, including lung cancer, ovarian cancer, colon cancer and melanoma. This expression reduces the sensitivity of tumor cells to cytotoxic T cell lysis mediated by specific T cell antigen receptors, leading to increased tumorigenicity and aggressiveness (34-36). CTLA-4, a member of the CD28-B7 immunoglobulin superfamily, is expressed on activated T cell surfaces, inhibiting their activity by competing with the costimulatory receptor CD28 for binding to B7-1 and B7-2, thereby downregulating immune responses (37). *In vivo*, anti-PD-1 and anti-CTLA-4 antibodies have varying immune effects, whether administered alone or in combination. CTLA-4 blockade primarily induced partial proliferation of transitional memory T cells in the blood/tumor tissue analysis of patients undergoing immune checkpoint blockade, whereas PD-1 blockade resulted in changes in cytolysis and NK-cell function-related genes. Blockade of both resulted in non-overlapping changes in gene expression patterns, including proliferation-related and chemokine genes (38). LAG3 comprises four external immunoglobulin superfamily domains in the cellular domain, a long linker peptide in the transmembrane domain, and a serine phosphorylation site in the intracellular domain. It is expressed on the surfaces of $CD4^+$, $CD8^+$, natural killer (NK), NKT and Treg cells, and inhibits T cell function. LAG3 is expressed in various tumors and is associated with patient prognosis. Blockade of LAG3 is also a new antitumor idea (39). TIM3 is an inhibitory checkpoint protein expressed on Th1, Th17, Tregs, $CD8^+$ T, NK and dendritic cells. It is associated with antitumor immunity, and blocking it is a promising approach to cancer therapy (40). IDO is an immunomodulatory enzyme that metabolizes the essential amino acid tryptophan to its downstream kynurenine, thereby inhibiting T cell immunity. Inhibiting IDO is also a way to enhance tumor immunity (32). Furthermore, there has been an increasing use of ICIs and targeted therapies in combination, such as anti-PD-1/PD-L1 and anti-CTLA-4 combination therapy, as well as anti-PD-1/PD-L1 and anti-vascular endothelial growth factor combination therapy (41). ICIs have achieved favorable results in clinical applications. However, some patients initially respond to ICIs therapy but later exhibit drug resistance, which is related to the abundant mutation function of tumor cells, enabling them to evade T cell-mediated immune surveillance once again (42). Moreover, the primary focus of immunotherapy is to enhance the immune activation mechanism. This 'immune enhancement' strategy often causes frequent irAEs, although with the advancement of immunotherapy and therapy design, related adverse events are being gradually reduced (43). Common adverse effects of CTLA-4 and/or PD-1 inhibition occur in the skin, gastrointestinal tract, liver and endocrine system, such as pruritus, rash, nausea, diarrhea and thyroid disorders (44). When irAEs occur in ICIs-treated patients, they may need to discontinue ICIs and treat irAEs, compromising treatment efficiency (45). The clinical studies conducted in previous years are included in Table I (46-61). In these clinical studies, a variety of common tumor types were included. Their efficacy in ICIs as monotherapy as in combination therapy is very limited. Response rates were modest, and a substantial proportion of patients developed grade 3-4 irAEs. Despite the progress made with ICIs, their inefficiency and the inevitability of irAEs remain significant challenges. Therefore, more treatment and prevention methods need to be developed to address the deficiencies of ICIs.

## 4. Gut microbiota and ICIs

*Application and mechanism of gut microbiota in the treatment of ICIs*. Recent studies have demonstrated that gut microbiota plays a crucial regulatory role in ICIs therapy, offering a novel approach to enhance the clinical effectiveness of ICIs. Assessing the gut microbiota of patients can provide guidance and regulation for the subsequent clinical implementation of ICIs (62-65). Previous studies exploring the association between gut microbes and ICIs are presented in Table II. Generally, patients with higher levels of *Firmicutes* and

Table I. Clinical studies of ICIs.

| Author/s | Year | Number of patients | ICI | Diagnosis | Trial name | Main conclusion | (Refs.) |
|---|---|---|---|---|---|---|---|
| Topalian *et al* | 2012 | 296 | BMS-936558, (anti-PD-1) | Advanced solid tumors | NCT00730639 | The ORR was ~1 in 4 to 1 in 5 and 14% of patients experienced grade 3 or 4 irAEs | (46) |
| Ott *et al* | 2017 | 75 | Pembrolizumab, (anti-PD-1) | Advanced endometrial cancer | NCT02054806 | The PR rates was achieved in 13.0% of the patients, and irAEs occurred in 54.2% of the patients | (47) |
| Antonia *et al* | 2019 | 304 | Durvalumab, (anti-PD-L1) | Stage IIIB-IV non-small cell lung cancer (NSCLC) | NCT01693562 | The ORR of patients with PD-L1 expression greater than or equal to 25% was 21.8%, and the ORR of patients with PD-L1 expression less than 25% was 6.4% irAEs occurred in 57.2% of patients | (48) |
| Schöffski *et al* | 2022 | 255 | Ieramilimab (anti-LAG-3) ± Spartalizumab (anti-PD-1) | Advanced solid tumors | NCT02460224 | Tumor responses occurred in 10% of patients. And irAEs occurred in 56 and 69% of patients in the ieramimab monotherapy and ieramimab plus Spartalizumab groups, respectively | (49) |
| Curigliano *et al* | 2021 | 219 | Sabatolimab (anti-TIM-3) ± Spartalizumab (anti-PD-1) | Advanced solid tumors | NCT02608268 | The partial response rates occurred in 6% of patients receiving combination therapy, and irAEs occurred in 48% | (50) |
| Kelly *et al* | 2023 | 30 | Epacadostat (anti-IDO1-) Pembrolizumab4 (anti-PD-1) | Advanced sarcoma | N | The ORR was 3.3, and 23% of patients experienced grade 3 irAEs | (51) |
| Zakharia *et al* | 2021 | 131 | Indoximod (anti-IDO1-) + Pembrolizumab4 (anti-PD-1) | Advanced melanoma | N | The ORR of the evaluable population was 51%, and the most common irAE was fatigue, with an incidence of 62.3% | (52) |
| Lynch *et al* | 2012 | 204 | Ipilimumab (anti-CTLA-4) + Paclitaxel and Carboplatin | Stage IIIB/IV NSCLC | N | The immune-related best response rates for staged ipilimumab, concurrent ipilimumab, and control therapy were 32, 21, and 18%, respectively. The overall incidence of grade 3 and 4 irAEs was 15, 20, and 6% in the staged ipilimumab, concurrent ipilimumab, and control groups, respectively | (53) |

Table I. Continued.

| Author/s | Year | Number of patients | ICI | Diagnosis | Trial name | Main Conclusion | (Refs.) |
|---|---|---|---|---|---|---|---|
| Wolchok *et al* | 2018 | 945 | Ipilimumab (anti-CTLA-4) ± Nivolumab (anti-PD-1) | Advanced melanoma | N | At 3 years, the OS rates were 58% with nivolumab plus ipilimumab, 52% with nivolumab alone, and 34% with ipilimumab alone | (54) |
| Hellmann *et al* | 2018 | 2,877 | Ipilimumab (anti-CTLA-4) + Nivolumab (anti-PD-1) | Stage IV or recurrent NSCLC | NCT02477826 | The ORR for nivolumab plus ipilimumab was 45.3%, and the incidence of grade 3 or 4 irAEs related to nivolumab plus ipilimumab was 31.2% | (55) |
| Tannir *et al* | 2021 | 1,096 | Ipilimumab (anti-CTLA-4) + Nivolumab (anti-PD-1) vs. Sunitinib | Advanced renal cell carcinoma with sarcomatoid features | N | The ORR with ipilimumab plus nivolumab was 60.8%, and grade 3 or 4 irAEs occurred in 49% | (56) |
| Rini *et al* | 2019 | 915 | Atezolizumab (anti-PD-L1) + Bevacizumab vs. Sunitinib | Metastatic renal cell carcinoma | NCT02420821 | Grade 3-4 irAEs occurred in 40% of the atezolizumab plus bevacizumab group | (57) |
| Garon *et al* | 2019 | 550 | Pembrolizumab (anti-PD-1) | Advanced programmed PD-L1 NSCLC | N | The estimated 5-year OS was 23.2% for treatment-naive patients and 15.5% for previously treated patients, and the incidence of irAEs was 71% | (58) |
| Yuan *et al* | 2023 | 72 | Camrelizumab (anti-PD-1) + Apatinib | Recurrent/metastatic nasopharyngeal carcinoma | NCT04547088 NCT04548271 | The ORR of the platinum-resistant cohort was 65%, and the ORR of the PD-1 inhibitor-resistant cohort was 34.3, and 65.3% of the patients developed ≥ grade 3 irAEs | (59) |
| Liu *et al* | 2023 | 20 | Camrelizumab (anti-PD-1) + Apatinib | Relapsed or refractory peripheral T-cell lymphoma | N | The ORR for all patients was 30%, and grade 3 or higher adverse events were hyperlipidemia (15%), hypokalemia (15%), and anemia (15%) | (60) |
| Zhao *et al* | 2023 | 53 | Cadonilimab (anti PD-1 and CTLA-4 bispecific antibody) | Metastatic NSCLC | NCT04172454 | The ORR of patients who had previously received platinum-based two-agent chemotherapy failure was 10, and 11.3% of patients had grade 3-4 irAEs | (61) |

ICI, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed cell cell death protein ligand 1; PFS, progression-free survival; NSCLC, non-small cell lung cancer; OS, overall survival. ORR, objective response rate; PR, partial response.

Table II. Gut microbiota and ICIs.

| Author | Year | Categories of study | Gut microbiota | Study summary | (Refs.) |
|---|---|---|---|---|---|
| Vétizou *et al* | 2015 | Animal study | *Bacteroides thetaiotaomicron*, *Bacteroides fragilis* | *Bacteroides thetaiotaomicron* or *Bacteroides fragilis* can overcome the condition that tumors from antibiotic-treated or germ-free mice do not respond to anti-cytotoxic T lymphocyte antigen-4 | (65) |
| Routy *et al* | 2017 | Animal study | *Akkermansia muciniphila* | Increased relative abundance of *Akkermansia muciniphila* could increase anti-PD-1 efficacy | (67) |
| Grenda *et al* | 2022 | Clinical study | *Akkermansiaceae* | Patients with higher abundance of *Akkermansiaceae* had favorable response to anti-PD-1 or anti-PD-L1 treatment | (68) |
| Grenda *et al* | 2022 | Clinical study | *Bacteroidaaceae, Barnesiellaceae, Tannerellaceae* | *Bacteroidaaceae*, *Barnesiellaceae* and *Tannerellaceae* could prolong PFS in patients with NSCLC treated with ICIs | (69) |
| Newsome *et al* | 2022 | Clinical and animal study | *Ruminococcus, Akkermansia, Faecalibacterium* | *Ruminococcus*, *Akkermansia* and *Faecalibacterium* were significantly enriched in responders of NSCLC treated with ICIs | (70) |
| Lee *et al* | 2022 | Clinical study | *Bifidobacterium pseudatenulatum, Roseburia spp. Akkermansia muciniphila* | *Bifidobacterium pseudatenulatum*, *Roseburia spp.* and *Akkermansia muciniphila*, were associated with response to ICIs in patients with advanced cutaneous melanoma | (71) |
| Xu *et al* | 2020 | Animal study | *Prevotella_sp._CAG:485, Akkermansia* | *Prevotella_sp._CAG:485* and *Akkermansia* improved anti-PD-1 efficacy | (73) |
| Peiffer *et al* | 2022 | Clinical study | *Akkermansia muciniphilia* | Lower levels of *Akkermansia muciniphilia* were observed in advanced metastatic castrate resistant prostate cancer responders treated with pembrolizumab | (74) |
| Gopalakrishnan *et al* | 2018 | Clinical study | *Ruminococcaceae* | The α diversity of gut microbes and the relative abundance of *Ruminococcaceae* bacteria were significantly higher in melanoma responders than in non-responders on anti-PD-1 therapy | (75) |
| Matson *et al* | 2018 | Clinical study | *Bifidobacterium longum, Collinsella aerofaciens, Enterococcus faecium* | *Bifidobacterium longum*, *Collinsella aerofaciens* and *Enterococcus faecium* were more abundant in the gut microbiota of melanoma responders treated with anti-PD-1 | (76) |
| Hakozaki *et al* | 2020 | Clinical study | Ruminococcaceae *UCG 13*, *Agathobacter* | Enrichment of *Ruminococcaceae UCG 13* and *Agathobacter* is associated with favorable objective response rate and PFS in NSCLC patients treated with ICIs | (77) |
| Jin *et al* | 2019 | Clinical study | *Alistipes putredinis, Bifidobacterium longum, Prevotella copri, Ruminococcus* | The gut microbiota of NSCLC patients who responded to anti-PD-1 therapy was enriched for *Alistipes putredinis*, *Bifidobacterium longum*, and *Prevotella copri*, whereas *Ruminococcus* was enriched in non-responders | (78) |
| Mao *et al* | 2021 | Clinical study | *Ruminococcus calidus*, Erysipelotichaceae *bacterium-GAM147*, Veillonellaceae | In anti-PD-1 therapy for non-resectable hepatocellular carcinoma or advanced biliary tract cancers, Patients with higher abundance of *Ruminococcus calidus* and *Erysipelotichaceae bacterium-* | (79) |

Table II. Continued.

| Author | Year | Categories of study | Gut microbiota | Study summary | (Refs.) |
|---|---|---|---|---|---|
| | | | | *GAM147* had longer PFSand OS, whereas those with higher abundance of *Veillonellaceae* had worse PFS and OS | |
| Shen *et al* | 2021 | Clinical study | *Bifidobacterium*, *Coprococcus*, *Acidaminococcus* | The enrichment of *Bifidobacterium*, *Coprococcus* and *Acidaminococcus* was associated with the efficiency of ICIs treatment in patients with hepatocellular carcinoma | (80) |
| Wang *et al* | 2021 | Clinical study | *Fusobacterium* | *Fusobacterium* was more abundant in colorectal cancer patients who did not respond to anti-PD-1 treatment | (81) |

ICI, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; NSCLC, non-small cell lung cancer; OS, overall survival.

*Verrucomicrobiota* in their gut microbiota exhibited a more favorable response to ICIs, whereas those with an abundance of Proteobacteria showed a diminished response. The relationship between *Bacteroidetes* and treatment response was found to be varied. Regarding the occurrence of adverse reactions, *Firmicutes* exhibited higher levels, whereas *Bacteroidetes* displayed lower levels. Furthermore, the administration of antibiotics is typically negatively correlated with the clinical response to ICIs (66). A previous study encompassing clinical and animal research demonstrated a correlation between clinical responses to ICIs targeting the PD-1/PD-L1 axis and the relative abundance of *Akkermansia muciniphila* (67). An investigation into the impact of ICIs treatment on patients with non-small cell lung cancer (NSCLC) revealed a higher prevalence of *Akkermansiaceae* in individuals demonstrating stable disease and partial response to immunotherapy, as opposed to those with progressive disease (68). The study conducted by Grenda *et al* (69) demonstrated that *Bacteroidaaceae*, *Barnesiellaceae* and *Tannerellaceae* were capable of extending progression-free survival (PFS) in patients with NSCLC. Newsome *et al* (70) obtained similar results in their study involving patients with stage III/IV NSCLC who received ICIs treatment, revealing significant enrichment of *Ruminococcus*, *Akkermansia* and *Faecalibacterium* among responders. In the context of melanoma-based ICIs therapy, response was also linked to *Bifidobacterium pseudatenulatum*, *Roseburia spp.* and *Akkermansia muciniphila* (71). The aforementioned multiple similar studies demonstrated the more favorable effects of *Akkermansia muciniphila* on ICIs. *Akkermansia muciniphila*, a strictly anaerobic gut bacterium, thrives on intestinal mucin as its exclusive carbon and nitrogen source, colonizing the intestine in a manner intricately linked to the host's well-being. It regulates the immune response of the organism, sustains metabolic equilibrium, ameliorates obesity, type 2 and type 1 diabetes, hepatic steatosis, intestinal inflammation, and augments responses of ICIs across various cancer types (72). Concerning the mechanism underlying the treatment of ICIs by *Akkermansia muciniphila*, an animal experiment revealed that *Akkermansia* can modulate the therapeutic capacity of PD-1 antibodies in mice with colorectal cancer by influencing the metabolism of glycerophospholipid and the expression of immune-related cytokines (IFN-γ and IL-2) within the tumor microenvironment, thus preserving the normal effectiveness of PD-1 antibodies (73). However, a recent study examining the association between gastrointestinal microbiome composition and ICIs in advanced metastatic castration-resistant prostate cancer found a decrease in levels of *Akkermansia muciniphilia* in response samples, which contradicts previous findings in other types of tumors. The aforementioned study observed a correlation between the abundance of *Streptococcus salivarius* in fecal samples and treatment response. It is possible that tumor type is also associated with the mechanisms through which gut microbiota affect ICIs' therapy (74). Additionally, the study design and potential confounding factors may have contributed to these findings. A study conducted with melanoma patients undergoing anti-PD-1 treatment revealed significant disparities in the diversity and composition of the gut microbiota between individuals who responded to the treatment and those who did not. Responders exhibited significantly higher

alpha diversity of gut microbiota and greater relative abundance of *Ruminococcaceae* compared with non-responders. Moreover, fecal transplantation from responders enhanced antitumor immunity in mice (75). Another analogous study, focusing on patients undergoing ICIs treatment for melanoma, demonstrated the abundance of certain bacterial species, such as *Bifidobacterium longum*, *Collinsella aerofaciens* and *Enterococcus faecium*, in individuals who responded to the treatment (76). A study conducted on ICIs in advanced NSCLC demonstrated that the α diversity of gut microbiota was correlated with overall survival (OS), while the presence of *Ruminococcaceae UCG 13* and *Agathobacter* revealed a positive association with favorable objective response rate and PFS (77). In Chinese patients with NSCLC who underwent anti-PD-1 treatment, the gut microbiota exhibited enrichment of *Alistipes putredinis*, *Bifidobacterium longum* and *Prevotella copri* in the responder group, while *Ruminococcus* was enriched in the non-responder group. Additionally, patients with a higher diversity of gut microbiota demonstrate an enhanced tumor-killing effect when undergoing anti-PD-1 treatment (78). In a study examining the correlation between clinical response to anti-PD-1 therapy and gut microbiota in patients with advanced hepatobiliary cancer, individuals with a higher abundance of *Lachnospiraceae bacterium-GAM79* and *Alistipes sp. Marseille-P5997* demonstrated longer PFS and OS compared with those with lower abundance. Furthermore, a high abundance of *Ruminococcus calidus* and *Erysipelotichaceae bacterium-GAM147* was linked to extended PFS and improved treatment response. Conversely, patients with higher abundance of *Veillonellaceae* exhibited poorer PFS and OS (79). Another study investigating the gut microbiota in patients with hepatocellular carcinoma and their response to ICIs revealed an enrichment of *Bifidobacterium*, *Coprococcus* and *Acidaminococcus* in patients with disease control (80). However, the initial abundance of these three taxa did not predict an OS benefit in the aforementioned study. In a study investigating the combination of regorafenib and toripalimab for colorectal cancer, a higher relative abundance of *Fusobacterium* was linked to lack of response and shorter PFS (81). Additionally, a previous study provided evidence that *Helicobacter pylori* infection can upregulate the expression of PD-L1 in human gastric epithelial cells. Further investigation into its clinical significance is warranted (82). According to Park *et al* (83), the mechanism through which gut microbiota influence ICIs involves the downregulation of PD-L2 and its binding partner, repulsive guidance molecule b, thereby enhancing the efficacy of anti-PD-1 treatment. Ongoing studies in this field are continuously being conducted. Generally, future research should focus on investigating the individual species and overall distribution of gut microbiota. The conclusions of the previous studies are not consistent, which may be attributed to differences in study design, tumor type, sample size and potential confounding factors. Among the aforementioned studies, some are animal studies, some are clinical studies, and the tumor types are not exactly the same. In addition, the sample size was between tens to hundreds, with large differences. Finally, confounding factors such as sex, height, weight, diet and ethnicity can further affect the results of experiments. Nevertheless, certain specific species and characteristics of gut microbiota, such as a higher abundance of *Akkermansia* and greater α diversity, have demonstrated a positive effect on ICIs in multiple studies. These findings warrant further exploration as important avenues for future research.

*Gut microbiota-associated metabolites and ICIs*. The role of gut microbiota in the treatment of ICIs may be attributed to their associated metabolites. A study conducted on patients with gastrointestinal cancers receiving anti-PD-1/PD-L1 therapy revealed that those who exhibited a higher *Prevotella/Bacteroides* ratio or higher abundance of *Prevotella*, *Ruminococcaceae* and *Lachnospiraceae* demonstrated improved responses to anti-PD-1/PD-L1 therapy. These findings may be linked to the metabolites produced by the gut microbiota. Specifically, gut microbiota capable of producing SCFAs, such as *Eubacterium*, *Lactobacillus* and *Streptococcus*, were found to be positively associated with anti-PD-1/PD-L1 responses in gastrointestinal cancers (84). Another study focusing on patients with solid cancer tumors treated with anti-PD-1 therapy demonstrated that higher concentrations of certain SCFAs, including fecal acetic acid, propionic acid, butyric acid, valine and plasma isovaleric acid, were associated with longer PFS (85). The aforementioned study also suggested that SCFAs may serve as the link between gut microbiota and the efficacy of anti-PD-1 therapy. Furthermore, it was found that the gut microbiota metabolite butyrate can directly enhance the response of antitumor cytotoxic $CD8^+$ T cells *in vitro* and *in vivo* by promoting IL-12 signaling, thereby improving the efficacy of antitumor therapy (86). However, another study indicated that elevated levels of butyrate and propionate in the blood led to an increase in the proportion of Treg cells, which resulted in a diminished anti-CTLA-4 blockade effect and limited the activity of anti-CTLA-4 therapy (87). Additionally, a study focusing on ICIs for unresectable hepatocellular carcinoma demonstrated that ursodeoxycholic acid and ursocholic acid were significantly enriched in the feces of patients who exhibited an objective response, and these metabolites were correlated with the abundance of *Lachnoclostridium* (88). Jiang *et al* (89) study revealed that *Fusobacterium nucleatum* and increased succinic acid hindered the efficacy of anti-PD-1 therapy in patients with colorectal cancer. However, it is important to note that these studies have yielded conflicting conclusions, emphasizing the need for further exploration into the role of gut microbiota metabolites in ICIs treatment. Currently, there is no further study on how gut microbiota metabolites affect the efficiency of ICIs application by regulating the immune system. The underlying mechanisms are likely to be highly complex, involving interactions between different gut microbiota and various metabolites. Additionally, investigating the intricate mechanisms of downstream gene regulation, immune cell modulation, and regulation of inflammatory factors presents a significant challenge.

*Antibiotics and ICIs*. The use of antibiotics can affect the composition of gut microbiota, subsequently influencing the modulating role of gut microbiota in the effectiveness of ICIs. Generally, antibiotic treatment is associated with poor OS (90). The utilization of antibiotics emerged as an independent negative predictor of PFS and OS in patients with advanced cancer undergoing ICI treatment. Patients who

underwent repetitive or prolonged antibiotic use exhibited a poorer treatment response (91). In a retrospective analysis of nivolumab-treated patients with NSCLC, the median PFS was 1.2 months for patients receiving antibiotics compared with 4.4 months for those who did not, although no difference in OS was observed (92). Another study demonstrated that antibiotic use diminished PFS and OS in patients with advanced renal cell carcinoma and NSCLC, and it exacerbated disease progression in patients with renal cell carcinoma who received antibiotics within 30 days of commencing ICIs, in comparison with those who did not receive antibiotics (93). The mechanism underlying the impact of antibiotics on ICI effectiveness may lie in the disruption of gut microbiota's ecological stability, which compromises the immune homeostasis maintained by gut microbiota, subsequently leading to dysregulation of intestinal immune responses. At present, no further studies have examined how antibiotics specifically affect gut microbiota and the immune system to alter the efficiency of ICIs. This area requires further exploration. Nevertheless, based on the collective results of current studies, the use of antibiotics in patients receiving ICIs should be more strictly regulated to ensure the efficacy of ICIs.

*Gut microbiota regulates tumor proliferation*. Gut microbiota can directly impact tumors, regulating their occurrence and development. For instance, *Propionibacterium acidipropionici* and *Freudenreichii* produce cytotoxic compounds, namely SCFAs propionate and acetate, which induce apoptosis in colorectal cancer cell lines. Similarly, *Lactobacilli* stimulate immune response, and *Lactobacillus casei ATCC334* produces a killing effect on tumor cells through its metabolite ferrichrome (94). The probiotic LGG-SN selectively reduces cancer cell viability by inducing mitotic arrest in the G2/M phase of the cell cycle in tumor cells (29). On the contrary, *Fusobacterium nucleatum* activates beta-catenin through *Fusobacterium* adhesin A, and *Peptostreptococcus anaerobius* promotes tumor cell proliferation by activating the PI3K-Akt pathway in tumor cells and NF-κB activation in tumor-associated macrophages (94). SCFAs, which are common metabolites of gut microbiota, have demonstrated antitumor activity in various types of tumors. They control the proliferation and metastasis of colorectal, gastric, lung, cervical, breast and bladder cancer, and other common tumors through the regulation of epigenetic modifications, inhibition of tumor cell proliferation, and regulation of antitumor immunity (95). The impact of gut microbiota on tumor development is closely related to the tumor microenvironment. Gut microbiota and their metabolites modify the tumor microenvironment by preserving the integrity of the intestinal mucosal barrier, regulating inflammatory factors, and controlling immune cell activation, among other aspects. These mechanisms collectively limit the progression of tumors (96).

*Gut microbiota and irAEs and application of probiotics*. The relationship between irAEs and gut microbiota has been the subject of investigation in several studies. Andrews *et al* (97) demonstrated a significant association between a higher abundance of *Bacteroides* and irAEs in melanoma patients receiving ICIs. Another clinical trial evaluating ipilimumab for the treatment of metastatic melanoma found an inverse association between the increase of specific bacteria in the *Bacteroidetes* phylum and colitis after immunotherapy (98). Similarly, a study focusing on immune-related diarrhea in lung cancer patients treated with anti-PD-1 antibodies revealed that patients without diarrhea had higher levels of *Bacteroidetes* and lower levels of *Firmicutes* (99). At present, there are few studies on the relationship between gut microbiota and irAEs, no specific dominant bacteria have been found, and no studies have further elucidated the underlying mechanism. Further exploration of the relationship between irAEs and gut microbiota is warranted. The underlying mechanism may be linked to the unique properties of certain gut microbiota, necessitating further investigation. Future studies should aim to accurately identify and analyze the relationship between dominant strains and specific irAEs. Nevertheless, supplementing probiotics to modulate the microecological environment of gut microbiota may alleviate the occurrence of irAEs, particularly intestinal-related symptoms. Probiotic supplementation represents a clinical approach that capitalizes on the role of gut microbiota in ICI treatment. Sivan *et al* (100) animal study demonstrated that oral administration of *Bifidobacterium* alone achieved comparable melanoma control to anti-PD-L1 treatment. Proton pump inhibitors, which facilitate the migration of oral microbiota to the gut, generally have a negative effect on the efficacy of ICIs in cancer patients. In a trial involving advanced or recurrent patients with NSCLC treated with PD-1/PD-L1, treatment with *Clostridium butyricum MIYAIRI 588* (*CBM588*) improved the efficacy of ICIs in patients receiving proton pump inhibitors, potentially through modulation of specific microbiota richness (101). Another study revealed that *CBM588* supplementation increased the response rate and prolonged PFS in the treatment of metastatic renal cell carcinoma with nivolumab plus ipilimumab (102). Similarly, a retrospective analysis demonstrated that *CBM588* treatment significantly prolonged PFS and OS in patients with NSCLC treated with PD-1/PD-L1 (103). Probiotic supplementation also reduced immune-related intestinal inflammation. An animal study indicated that *Bifidobacterium* attenuated intestinal immunopathology in mice without significantly affecting anti-melanoma immunity induced by anti-CTLA-4 treatment (104). However, the role of probiotics in ICI treatment is not always beneficial. A clinical study involving patients with melanoma treated with ICIs suggested that higher dietary fiber intake was associated with significantly improved PFS, particularly in patients who consumed adequate dietary fiber without probiotic use. Consistent with findings in mice, low-fiber diets or probiotics (*Bifidobacterium longum*- or LGG) impaired anti-PD-1-based treatment responses (105). Gao *et al* (106) revealed that supplementation with *Lacticaseibacillus rhamnosus Probio-M9* enhanced the therapeutic efficiency in colorectal cancer of anti-PD-1 treatment through subsequent metabolism. This supplementation of probiotics may regulate the immune balance by producing beneficial metabolites such as SCFAs in the gut, thereby promoting the infiltration and activation of cytotoxic T lymphocytes and inhibiting the function of Tregs in the tumor microenvironment during ICI treatment. However, the effectiveness of probiotics in ICIs can be influenced by different types of probiotics used in various studies, different tumor types, and diverse patient populations. Inappropriate

supplementation can yield contradictory outcomes. Therefore, future research should focus on individualizing probiotic supplementation.

*Fecal transplantation*. Fecal transplantation is employed as a clinical approach to assess the role of gut microbiota in ICIs treatment. Fecal transplantation entails transferring stool from individuals who respond to non-responders' gut. An animal study demonstrated the superiority of combining fecal transplantation with anti-PD-1 therapy over either therapy alone (107). Experiments involving fecal transplantation of human-germ-free mice revealed that mice receiving response-derived fecal transplantation exhibited enhanced anti-tumor responses to anti-PD-L1 treatment compared with those receiving non-response-derived fecal transplantation (108). In clinical trials, Baruch *et al* (109) reported that out of 10 patients with refractory metastatic melanoma to anti-PD-1 therapy who underwent fecal transplantation from responders, 3 patients exhibited a clinical response. Another clinical study demonstrated that fecal transplantation from patients with melanoma who responded to anti-PD-1 therapy provided clinical benefit to 6 out of 15 patients with anti-PD-1 resistance (110). Moreover, fecal microbiota transplantation has been utilized to treat certain cases of ICIs-associated colitis, resulting in clinical benefit (111,112). Koo and Morrow (113) revealed individual variation in fecal dominant donor microbes among recipients following fecal transplantation, which is unrelated to the response to anti-PD-1 therapy. The success of fecal transplantation demonstrates the clinical feasibility of the gut microbiota's significant role in ICIs treatment. Patients who underwent fecal transplantation acquired a gut microecosystem that enhanced the efficacy of ICIs. However, the impact of fecal transplantation is highly limited and does not improve the non-response of the majority of patients to ICIs. This could be attributed to variations in the ecological environment of gut microbiota among individuals, thus suggesting the necessity for additional experiments to explore more precise methods in the application of fecal transplantation (114). Future research should address the need for more accurate donor selection, more effective gut microbiota transplantation methods, as well as the ethical challenges and potential risks associated with fecal transplantation.

## 5. Conclusion

ICIs have been extensively utilized in clinical practice for cancer therapy, and there is a growing body of evidence supporting the impact of gut microbiota on enhancing the effectiveness of ICIs treatment. The immune system, serving as the communication bridge between these entities, plays a pivotal role in their mechanism of action. ICIs primarily eliminate tumor cells by modulating the activation of the immune system, which is similarly influenced by gut microbiota. In general, gut microbiota, particularly symbiotic bacteria, primarily uphold immune tolerance to preserve their own ecological niche, whereas the principle of ICIs treatment operates in contrast. Conversely, the activation of the immune system by pathogenic bacteria may inflict harm on the body itself. Consequently, achieving a balance between gut microbiota and ICIs treatment may prove to be a highly intricate task. Nevertheless, this equilibrium could potentially serve as the pivotal factor in enhancing the efficiency of ICIs, thereby significantly impacting the prognosis of cancer patients. Currently, despite the ongoing nature of these investigations and the absence of definitive conclusions, the clinical utilization of probiotics and the exploration of fecal transplantation have provided additional perspectives supporting the viability of this approach (Fig. 1). Moving forward, future research can delve into the molecular intricacies of how gut microbiota and their downstream metabolites influence the efficacy of ICIs. Endeavoring to elucidate the precise mechanism underlying the maintenance of balance between gut microbiota and ICIs, as well as identify pivotal species. Ultimately, in clinical practice, precise and individualized implementation of specific probiotic supplementation and fecal transplantation is warranted to enhance the effectiveness of ICIs and optimize patient prognosis.

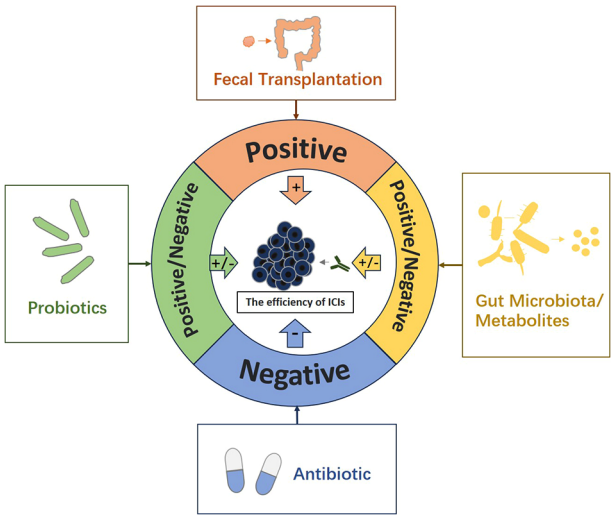


Figure 1. The role of gut microbiota in ICIs. Some members and characteristics of gut microbiota can enhance the efficiency of ICIs, while others can weaken it. According to different reports, some metabolites related to gut microbiota can enhance the efficiency of ICIs, while others can attenuate the efficiency of ICIs. The application of antibiotics in general attenuates the efficiency of ICIs. In general, the application of probiotics can enhance the efficiency of ICIs, but some studies have reported that the application of probiotics can weaken the efficiency of ICIs. Fecal transplantation can enhance the efficiency of ICIs. ICIs, immune checkpoint inhibitors.

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## Authors' contributions

HJ proposed the overall idea. HJ and QZ participated in the collection and collation of relevant data and the writing and

revision of the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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