

Faecal microbiota transplantation enhances efficacy of immune checkpoint inhibitors therapy against cancer

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Abstract

Even though immune checkpoint inhibitors (ICIs) are effective on multiple cancer types, there are still many non-responding patients. A possible factor put forward that may influence the efficacy of ICIs is the gut microbiota. Additionally, faecal microbiota transplantation may enhance efficacy of ICIs. Nevertheless, the data available in this field are insufficient, and relevant scientific work has just commenced. As a result, the current work reviewed the latest research on the association of gut microbiota with ICI treatments based on anti-programmed cell death protein 1 antibody and anti-cytotoxic T-lymphocyte-associated protein 4 antibody and explored the therapeutic potential of faecal microbiota transplantation in combination with ICI therapy in the future.

Key Words: Gut microbiome; Immunotherapy; Programmed cell death protein 1/programmed cell death protein ligand 1; Cytotoxic T-lymphocyte-associated protein 4; Immune checkpoint inhibitors resistance; Faecal microbiota transplantation

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Core Tip: Gut microbiota composition is closely associated with the efficacy of immune checkpoint inhibitors (ICIs). Specific species among the intestinal commensal bacteria may play a key role in the efficacy of ICIs against cancer. Faecal microbiota transplantation may enhance efficacy of ICIs.

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INTRODUCTION

Immune checkpoint molecules can modulate the immune system in the host *via* the transduction of immunosuppressive co-signals into the immunocompetent cells[1-5]. Typically, Programmed cell death protein 1 (PD-1)/programmed cell death protein ligand 1 (PD-L1) (CD274), PD-L2 (CD273), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4, CD152) are the most well-known examples[6-13]. These molecules are expressed in suitable cells at the suitable timing to exert their vital parts in the prevention of over-activated immune system in the host and the maintenance of immunological tolerance and homeostasis[1,2,5]. At the same time, immune checkpoint molecules show abnormal expression within tumour tissues[3,14-16]. Therefore, a strong immunosuppressive environment will be produced within tumour tissues, leading to resistance to treatment of numerous cancers. Immune checkpoint inhibitors (ICIs) mainly function to alleviate or destroy the immunosuppression mechanisms involved in tumour microenvironment (TME) by the use of inhibitory agents targeting the immune checkpoint molecules[2,5,17]. At present, anti-CTLA-4 (like ipilimumab), anti-PD-1 (such as pembrolizumab, nivolumab, and anti-PD-L1 (such as atezolizumab, durvalumab, avelumab) antibodies have been applied in treating several cancers in the word[18-23].

At present, checkpoint blockade still shows high effectiveness on certain cases, but just about 10%-30% cancers can achieve treatment responses. The combined used of ICIs is associated with a higher response rate and greater toxicity[24], regardless of the limited research on the ICI treatment. There are several ICI resistance mechanisms related to the low response rate, which are low PD-L1 expression, low tumour mutational burden, local immunosuppression, weak tumour cell antigenicity, tumour-infiltrating lymphocytes (TILs) functional exhaustion, no priming, and defected antigen presentation in the process of priming[25].

In addition, gut microbiome is suggested to be the potential factor that determines ICI efficacy. There are more than 100 trillion bacteria in the human gut, among which 500-1000 bacterial species have been identified to affect the mucosal immune system and exert vital parts in immune system operation under the normal or disease state [26]. Intestinal symbiotic bacteria may exert inflammatory or beneficial function while interacting with host immune system in intestinal lymphoid tissues. Therefore, faecal microbiota transplantation (FMT) can potentially improve the ICI efficacy. Nonetheless, there is only limited information on this topic, and related scientific work is merely at the beginning stage. The emergence of novel techniques has made it possible to investigate systemically the gut microbiota, which also sheds more light on the gut microbial compositions and their pathological variance. The present work aimed to review the latest research on the associations of gut microbiota with immune systems and ICI treatments based on anti-PD-1 antibody (Ab) and anti-CTLA-4 Ab and to explore the therapeutic potential of FMT combined with ICI therapy in the future.

ICIS

Two steps are necessary to activate tumour-specific T cells. Firstly, the selective binding of T cell receptor (TCR) to major histocompatibility complex I that has antigen-anchoring peptides[27]. Secondly, further amplification of the activation signal of TCR/CD3 complex is performed after the synergistic effect with co-stimulatory signals like OX40, CD28, and inducible T cell co-stimulator, which finally results in T cell priming and activation[27]. By contrast, co-inhibitory signals (also known as the immune checkpoints), including PD-1, CTLA-4, T cell immunoglobulin domain, mucin domain-3, and lymphocyte activation gene-3, inhibit T cell activation *via* offsetting CD28- or TCR/CD3-mediated tyrosine phosphorylation through the intracellular immunoreceptor tyrosine-based inhibition motif[28-30]. Tumour cells are likely to enhance the co-inhibitory signalling pathway activity for the sake of immune escape [31,32]. ICIs can decrease the tumour antigen immune tolerance and restore the anticancer response. Anti-CTLA-4 and anti-PD-1/PD-L1 are used to treat several cancers[33-38]. Nevertheless, there is a great potential to enhance the anticancer effect of ICI.

EFFECT OF GUT MICROBIOME ON THE EFFICACY OF ICIS

It has been recognized that gut microbiome is involved in cancer genesis and the immune surveillance that suppresses tumour progression[39-42]. Certain commensals may display the synergetic effects with treatments such as surgery, chemotherapy, radiotherapy, and immunotherapy after affecting the immune homeostasis in the intestine and immune adjustment of secondary immune organs[43-52]. ICIs can regulate tumour regression through enhancing the immune activation in the host. A series of studies suggested that gut microbiota composition shows close association with the efficacy of ICIs (Tables 1 and 2). At the same time, we revealed the potential mechanisms by which gut microbiome may be involved in the ICI efficacy (Figures 1 and 2).

Effect of gut microbiota on anti-PD-1/PD-L1 therapy

The PD-1/PD-L1 blockage treatment blocks the negative signals transduced by the PD-1 intracellular domains (like immunoreceptor tyrosine-based inhibition motif, immunoreceptor tyrosine-based switch motif)[53]. Typically, PD-1/PD-L1 blockage has been identified to promote T cell activation resulting from CD28 and TCR/CD3 while promoting T cell growth and survival by the activation of Ras-Raf-mitogen activated protein kinase and phosphatidylinositol 3 kinase-AKT signalling[54,55]. The PD-1/PD-L1 blockage treatment has been approved to treat certain malignant tumours, including non-small cell lung cancer (NSCLC), colorectal cancer (CRC), kidney cell cancer, and melanoma[56,57]. Biomarkers that contain the TIL status, PD-L1 expression, or deficiency of the mismatch repair system are tightly associated with the efficacy of PD-1/PD-L1 blockage treatment[58]. Besides those above-mentioned factors, gut microbiota contributes to difference in treatment responses as well[59].

In 2015, some investigators discover the relationship of gut microbiota with the efficacy of anti-PD-1 therapy using a mouse model[60]. Sivan *et al*[60] explored the therapeutic effect of anti-PD-1 therapy on C57BL/6 mice with genetic similarity, mice bearing the subcutaneous B16. SIY melanoma were obtained from two distinct mouse facilities [namely, Taconic Farms (TAC) and Jackson Laboratory (JAX)], which had markedly heterogeneous gut microbial compositions[60]. As a result, among the JAX populations, tumour growth was slower with higher sensitivity to the PD-1 blockage treatment. Such difference might be associated with the immune response. To be specific, JAX mice showed markedly enhanced CD8⁺ T cell aggregation within the tumour and tumour-specific T cell responses compared with the TAC counterparts. Further study suggested that the difference was abrogated by cohousing. In addition, when faecal microbiome was transferred from JAX to TAC, specific TILs increased and tumour development was suppressed. It was interesting that, in TAC, just the faecal microbiome transferred from JAX was able to suppress tumour development in the same degree with PD-1 blockage therapy, and it had synergistically regressed tumour development with PD-1 blockade therapy[60]. Gut microbiome analysis demonstrated that the abundance of *Bifidobacterium* was markedly increased in JAX. Meanwhile, the abundance of *Bifidobacterium* was significantly related to tumour specific immune cytotoxicity[60]. Administering the commercial *Bifidobacterium* cocktail (namely, *Bifidobacterium longum* and *Bifidobacterium breve*) significantly suppressed tumour growth, particularly when it was used in combination with the PD-1 blockage treatment[60]. It was suggested that such increased anticancer activity was associated with the higher interferon (IFN)- γ production, greater tumour-specific CD8⁺ T cell proportion, and alterations of dendritic cell (DC) functions[60].

Xu *et al*[61] investigated the roles of gut microbiome within the MSS-type mice bearing CRC that received diverse antibiotic treatments in the response to PD-1 Ab therapy. Following PD-1 Ab therapy, injecting antibiotics offset the therapeutic effect of PD-1 Ab on suppressing tumour development relative to control group[61]. Besides, control group showed enrichment of *Bacteroidales_S24-7* and *Bacteroides_sp._CAG:927*. At the same time, mice receiving colistin treatment showed enrichment of *Bacteroides_sp._CAG:927*, *Bacteroides* and *Prevotella_sp._CAG: 1031*, whereas mice receiving vancomycin treatment showed enrichment of *Akkermansia_muciniphila* and *Prevotella_sp._CAG:485*. For mice receiving vancomycin treatment, most metabolites were associated with the glycerophospholipid metabolic pathway, confirming to the metagenomic prediction pathway. Additionally, *Akkermansia* and *Prevotella_sp._CAG:485* contributed to maintaining the therapeutic effect of PD-1 Ab through impacting glycerophospholipid metabolism[61]. Gut microbial alteration resulted in alterations of the glycerophospholipid metabolism degree, thereby affecting immune cytokine expression [such as interleukin (IL)-2 and IFN- γ] within TME, giving rise to the diverse PD-1 Ab efficacy[61]. The above results reveal that gut microbial alter-

Table 1 Changes in microbiota composition associated with anti-programmed cell death protein 1/programmed cell death protein ligand 1 treatment efficacy against cancer and potential strategies for improving efficacy

Models	Disease	Implicated microbiota	New strategies	Implicated microbiota	Ref.
Mice	Melanoma	<i>Bifidobacterium</i> ↑	(1) FMT; and (2) Commercial cocktail of <i>Bifidobacterium</i> including <i>Bifidobacterium breve</i> and <i>B. longum</i>	NO	Sivan <i>et al</i> [60], 2015
Mice	CRC	<i>Bacteroides</i> _sp._CAG:927↑, <i>Bacteroidales</i> _S24-7↑, <i>Akkermansia muciniphila</i> ↑	NO	NO	Xu <i>et al</i> [61], 2020
Mice	CT26 tumours	NO	GQD	<i>s__Bacteroides acidifaciens</i> ↑, <i>s__uncultured_organism_g__norank_f__Bacteroidales_S24-7</i> ↑	Lv <i>et al</i> [62], 2019
Mice	RCC	NO	(1) FMT; (2) <i>A. muciniphila</i> ; and (3) <i>Bacteroides salyersiae</i>	NO	Derosa <i>et al</i> [66], 2020
Mice	Melanoma	NO	FMT	NO	Matson <i>et al</i> [68], 2018
Mice	MCA-205 sarcoma	NO	(1) FMT; (2) <i>A. muciniphila</i> ; and (3) <i>A. muciniphila</i> with <i>Enterococcus hirae</i> ; <i>Alistipes indistinctus</i>	NO	Routy <i>et al</i> [69], 2018
Mice	(1) RET; and (2) Melanoma	NO	(1) <i>A. muciniphila</i> ; and (2) <i>A. muciniphila</i> with <i>Enterococcus hirae</i> ;	NO	Routy <i>et al</i> [69], 2018
Human	NSCLC	<i>Parabacteroides</i> ↑, <i>Methanobrevibacter</i> ↑, <i>Veillonella</i> ↓, <i>Selenomonadales</i> ↓, <i>Negativicutes</i> ↓	NO	NO	Song <i>et al</i> [63], 2020
Human	NSCLC	Gut microbial diversity↑, <i>Alistipes putredinis</i> ↑, <i>B. longum</i> ↑, <i>Prevotella copri</i> ↑, <i>Ruminococcus unclassified</i> ↓	NO	NO	Jin <i>et al</i> [64], 2019
Human	NSCLC	Altered gut microbiota metabolome	NO	NO	Botticelli <i>et al</i> [65], 2020
Human	RCC	<i>A. muciniphila</i> ↑, <i>Bacteroides salyersiae</i> ↑, <i>Clostridium hathewayi</i> ↓	NO	NO	Derosa <i>et al</i> [66], 2020
Human	Melanoma	Gut microbial diversity↑, <i>Clostridiales/Ruminococcaceae</i> ↑, <i>Faecalibacterium</i> ↑, <i>Anaerotruncus colihominis</i> ↓, <i>Bacteroides thetaiotaomicron</i> ↓, <i>Escherichia coli</i> ↓	NO	NO	Gopalakrishnan <i>et al</i> [67], 2018
Human	Melanoma	<i>Bifidobacterium adolescentis</i> ↑, <i>B. longum</i> ↑, <i>Collinsella aerofaciens</i> ↑, <i>Enterococcus faecium</i> ↑, <i>Klebsiella pneumoniae</i> ↑, <i>Lactobacillus species</i> ↑, <i>Parabacteroides merdae</i> ↑, <i>Veillonella parvula</i> ↑, <i>Ruminococcus obeum</i> ↓, <i>Roseburia intestinalis</i> ↓	NO	NO	Matson <i>et al</i> [68], 2018
Human	NSCLC and RCC	<i>A. muciniphila</i> ↑	NO	NO	Routy <i>et al</i> [69], 2018
Human	Melanoma	NO	FMT	NO	Baruch <i>et al</i> [83], 2021

NO: No test or no research; FMT: Faecal microbiota transplantation; CRC: Colorectal cancer; RCC: Renal cell carcinoma; NSCLC: Non-small cell lung cancer; GQD: Gegen Qinlian decoction.

ations have certain impacts on the glycerophospholipid metabolic pathway, thus modulating the efficacy of PD-1 Ab immunotherapy in treating MSS-type mice bearing CRC.

Table 2 Changes in microbiota composition associated with anti-cytotoxic T-lymphocyte-associated protein 4 efficacy treatment against cancer and potential strategies for improving efficacy

Models	Disease	Implicated microbiota	New strategies	Implicated microbiota	Ref.
Mice	MCA205 sarcomas	<i>Clostridiales</i> ↑, <i>Bacteroides thetaiotaomicron</i> ↑, <i>B. uniformis</i> ↑, <i>Bacteroidales</i> ↓, <i>Burkholderiales</i> ↓,	(1) <i>B. thetaiotaomicron</i> ; (2) <i>B. fragilis</i> ; and (3) <i>Burkholderia cepacia</i>	NO	Vétizou <i>et al</i> [70], 2015
Mice	CRC	NO	<i>Lactobacillus acidophilus</i> cell lysates	NO	Zhuo <i>et al</i> [73], 2019
Mice	CRC	NO	(1) <i>Bifidobacterium pseudolongum</i> ; (2) <i>Lactobacillus johnsonii</i> ; (3) <i>Olsenella spp</i> ; and (4) Metabolite inosine	NO	Mager <i>et al</i> [74], 2020
Huamn	Melanoma	<i>Faecalibacterium genus</i> ↑, unclassified <i>Ruminococcus</i> ↑, <i>Lachnospiraceae genus</i> ↑, <i>Clostridium XIVa</i> ↑, <i>Blautia</i> ↑, Butyrate producing bacterium↑, <i>Gemmiger formicilis</i> ↑, <i>Bacteroides</i> ↓, <i>B. fragilis</i> ↓, <i>B. thetaiotaomicron</i> ↓	NO	NO	Chaput <i>et al</i> [72], 2017

NO: No test or no research; CRC: Colorectal cancer.

Recently, Lv *et al*[62] discovered that when Gegen Qinlian decoction (GQD) (one of the representative traditional Chinese medicine prescriptions) was used in conjunction with the anti-mouse PD-1 therapy in the xenograft model, it had potent effect on suppressing CT26 tumour growth. Besides, analysis on the gut microbiota also suggested that GQD used in combination with anti-mouse PD-1 therapy markedly enriched *s__uncultured_organism_g__norank_f__Bacteroidales_S24-7_and_s__Bacteroides_acidifaciens* group[62]. As indicated by metabolomic analysis results, metabolites with profound changes were detected in the combined treatment group [62]. Furthermore, the sphingolipid metabolism and glycerophospholipid metabolism metabolic pathways were examined[62]. Particularly, GQD combined with anti-mouse PD-1 treatment markedly promoted the fraction of CD8⁺ T cell subset within tumour tissue and peripheral blood samples and up-regulated IFN- γ level (an important factor of the anticancer immunotherapy)[62]. Moreover, GQD combined with anti-mouse PD-1 treatment decreased PD-1 expression while increasing IL-2 expression, revealing that such combined treatment suppressed the inhibitory checkpoints to restore efficiently T-cell functions[62]. Taken together, such findings revealed that GQD remodels gut microbiota to promote the anti-CRC efficacy of PD-1 blockade, and microsatellite stability was achieved.

Inspired by these results obtained from mouse models, many articles have been conducted to examine the association of gut microbiota with anti-PD-1 therapy among cancer cases. Song *et al*[63] explored the association of gut microbial structure and metabolomic features in the context of NSCLC with the anti-PD-1 therapy efficacy. According to analysis results of gut microbiome, cases from progression-free survival (PFS) \geq 6-mo group showed markedly increased β -diversity within gut microbiota relative to that of PFS < 6-mo group[63]. Besides, those from PFS \geq 6-mo group showed enrichment of *Methanobrevibacter* and *Parabacteroides*, whereas those from PFS < 6-mo group showed enrichment of *Selenomonadales*, *Negativicutes*, and *Veillonella*[63]. Furthermore, the protein families of function groups were studied using the COG, CAZy, and KO databases. As a result, 264, 859, and 390 functional groups were enriched in the above three databases, respectively, and significant differences were detected between the two groups. As revealed by analysis on bacterial metabolites, differences in the metabolic potentials of methane and methanol were significant between the two groups[63].

Jin *et al*[64] examined the association of gut microbiome with the clinical outcomes among the Chinese NSCLC cases receiving the anti-PD-1 therapy. Thereafter, patients were grouped as non-responder and responder groups based on the clinical response evaluated by the Response Evaluation Criteria in Solid Tumor version 1.1[64]. As a result, responders showed a greater gut microbial diversity at the beginning and stable composition in the process of treatment[64]. Besides, those showing higher microbial diversity were associated with the remarkably longer PFS in comparison with patients showing a lower diversity[64]. Differences in composition were detected between both groups, among which, *Alistipes putredinis*, *Prevotella copri*, and *Bifidobacterium longum* were enriched in responder group, while *Ruminococcus unclassified* was enriched in non-responder group[64]. In addition, the author applied multicolor flow cytometry to

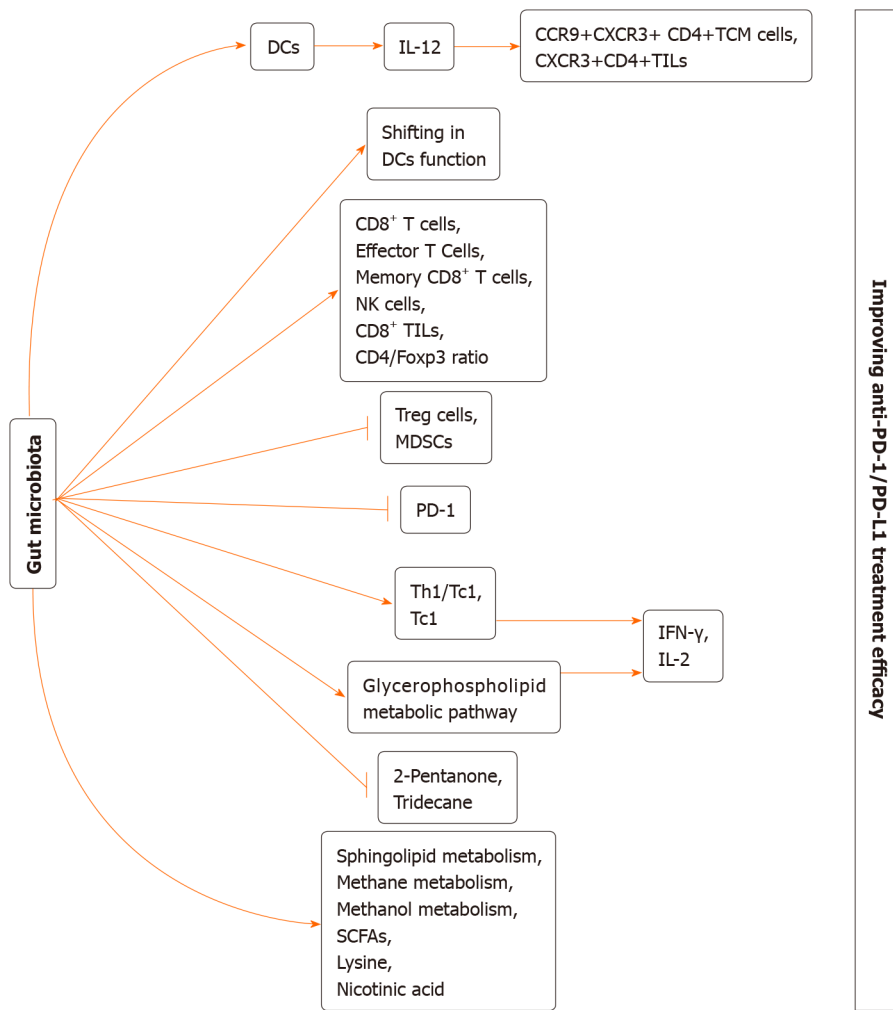


Figure 1 The potential mechanism of gut microbiome regulating anti-programmed cell death protein 1/programmed cell death protein ligand 1 treatment efficacy. (1) Gut microbiota may increase interleukin (IL)-12 production by dendritic cells (DCs), thereby increasing the CCR9⁺CXCR3⁺CD4⁺ central memory T cells and CXCR3⁺CD4⁺ tumour-infiltrating lymphocytes (TILs); (2) Gut microbiota may shift in the function of DCs; (3) Gut microbiota may increase CD8⁺ T cells, effector T Cells, memory CD8⁺ T cells, natural killer cells, CD8⁺ TILs, and CD4/Foxp3 ratio; (4) Gut microbiota may decrease numbers of regulatory T cells and myeloid-derived suppressor cells; gut microbiota may downregulate programmed cell death protein 1 expression; (5) Gut microbiota may induce Th1/Tc1 and Tc1 immune response, thereby increasing the interferon- γ and IL-2 secretion; (6) Gut microbiota may enhance glycerophospholipid metabolic pathway, thereby increasing the interferon- γ and IL-2 secretion; (7) Gut microbiota may decrease 2-pentanone and tridecane production; and (8) Gut microbiota may increase sphingolipid metabolism, methane metabolism, methanol metabolism, short chain fatty acids production, lysine production and nicotinic acid production. Altogether, all of these approaches may eventually improve anti-programmed cell death protein 1-1/programmed cell death protein ligand 1 treatment efficacy. DCs: Dendritic cells; T_{CM}: Central memory T; Treg: Regulatory T; MDSCs: Myeloid-derived suppressor cells; SCFAs: Short chain fatty acids; PD-1: Programmed cell death protein 1; IFN- γ : Interferon.

analyzed the systemic immune responses, which suggested that patients showing a greater gut microbial diversity were associated with higher proportions of peripheral blood natural killer cell and unique memory CD8⁺ T cell subsets upon anti-PD-1 treatment[64]. Botticelli and coworkers[65] also investigated the impact of gut microbial metabolome on anti-PD-1 therapy efficacy among NSCLC cases. As a result, 36% cases presented early progression, whereas the rest 64% showed progression at 12 mo later[65]. Besides, as revealed by gut microbiota metabolomic profiling, tridecane (alkane) and 2-Pentanone (ketone) were tightly related to early progression; by contrast, nicotinic acid, lysine and short chain fatty acids (namely, butyrate, propionate) were closely related to long-term benefits[65].

Recently, Derosa *et al*[66] assessed the significance of faecal bacterial composition in the anti-PD-1 treatment effect among patients with advanced renal cell carcinoma (RCC). Relative to RCC cases who received PD-1 blockage treatment with no use of antibiotics, RCC cases who received anti-PD-1 treatment in the presence of antibiotic treatment had evidently decreased objective response rates, which remarkably impacted the microbial composition. As a result, certain species like *Clostridium hathewayi* were dominant, and their abundances were higher in faecal samples of RCC cases relative to normal subjects. Tyrosine kinase inhibitors administered before

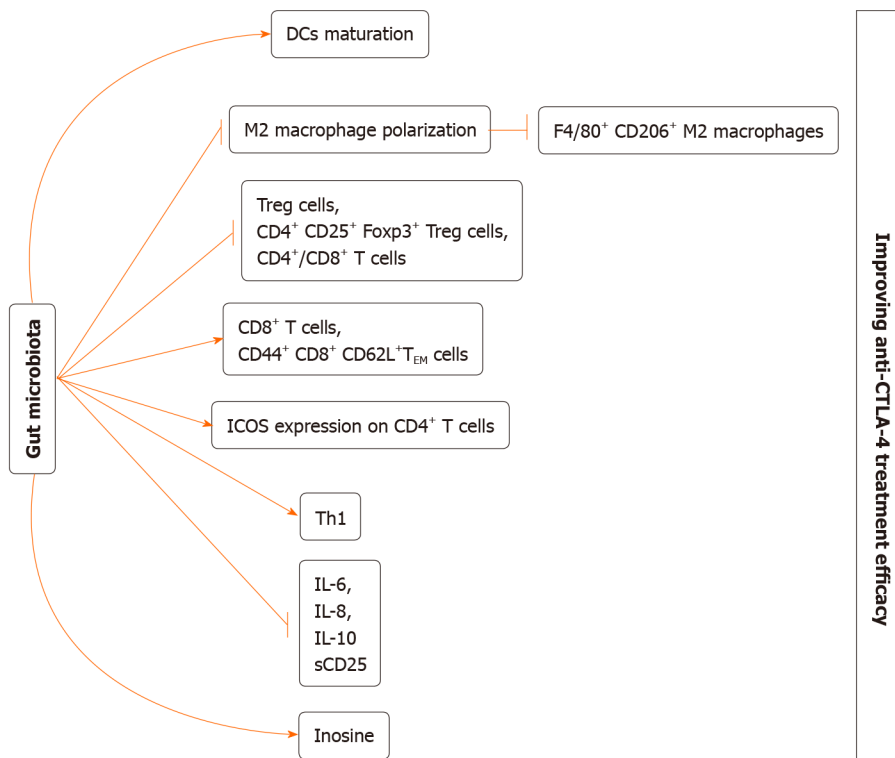


Figure 2 The potential mechanism of gut microbiome regulating anti-cytotoxic T-lymphocyte-associated protein 4 treatment efficacy. (1) Gut microbiota may induce dendritic cells maturation; (2) Gut microbiota may inhibit the M2 polarization, thereby decreasing M2 macrophages (F4/80⁺CD206⁺); (3) Gut microbiota may decrease regulatory T cells, CD4⁺CD25⁺Foxp3⁺ regulatory T cells, and CD4⁺/CD8⁺ T cells; (4) Gut microbiota increase CD8⁺ T cells and CD44⁺CD8⁺CD62L⁺ effector memory T cells; (5) Gut microbiota may increase inducible T cell co-stimulator expression on CD4⁺ T cells; (6) Gut microbiota may induce T helper 1 immune response; (7) Gut microbiota may reduce interleukin (IL)-6; IL-8; IL-10, and sCD25 level; and (8) Gut microbiota may increase inosine production. Altogether, all of these approaches may eventually improve anti- cytotoxic T-lymphocyte-associated protein 4 treatment efficacy. DCs: Dendritic cells; Treg: Regulatory T; T_{EM}: Effector memory T cells; ICOS: Inducible T cell co-stimulator; sCD25: Soluble CD25; IL: Interleukin.

nivolumab were related to the shift of microbial composition. For establishing the cause-effect relation of gut microbial composition with the anti-PD-1 therapy efficacy, some preclinical studies discovered that RCC-bearing mice receiving FMT from RCC cases developed resistance to anti-PD-1 therapy (NR-FMT). At the same time, both beneficial commensals (*Bacteroides salyersiae* and *A. muciniphila*) verified through whole genome sequencing and FMT successfully compensated the NR-FMT mice.

Conforming to the above results, Gopalakrishnan *et al*[67] evaluated the gut microbiota in melanoma cases who received the PD-1 blockage treatment (faecal samples from 43 cases, including 13 non-responders and 30 responders). As a result, responders exhibited a greater gut microbial diversity. Besides, in faecal samples, α -diversity showed positive correlation with PFS[67]. Further analysis indicated that the level of Clostridiales/Ruminococcaceae, *Faecalibacterium* (belonging to the Ruminococcaceae family, Clostridiales order) was higher in responders, while *Anaerotruncus colihominis*, *Bacteroides thetaiotaomicron* (belonging to Bacteroidales order), and *Escherichia coli* were significantly enriched in non-responders[67]. Additionally, the abundance of *Faecalibacterium* and Bacteroidales showed positive and negative relationships with tumour infiltrating CD8⁺ T cell level, respectively. The high abundances of *Faecalibacterium*, Ruminococcaceae, and Clostridiales in peripheral blood were accompanied with the increased effector T cell proportion, whereas Bacteroidales abundance showed positive relationship with regulatory T cells (Tregs) and myeloid-derived suppressor cell proportions. As revealed by multiple immunohistochemistry analyses, there were greater abundances of immune markers enriched in *Faecalibacterium* of the melanoma cases[67]. Such conclusions were verified by FMT experiments carried out in mouse models[67]. Matson *et al*[68] also found that gut microbiota affected anti-PD-1 therapy efficacy among the melanoma cases who developed metastasis. Meanwhile, as suggested by gut microbial analysis, the abundances of *B. longum*, *Bifidobacterium adolescentis*, *Enterococcus faecium*, *Collinsella aerofaciens*, *Lactobacillus* species, *Klebsiella pneumoniae*, *Veillonella parvula*, and *Parabacteroides merdae* were higher among responders, whereas those of *Roseburia intestinalis* and *Ruminococcus obeum* were significantly higher among the non-responders[68]. In addition, germ-free (GF) mice

subjected to gavage with responders-derived faecal materials showed significantly elevated IFN- γ and CD8⁺TIL levels and suppressed tumour growth, which facilitated to form the immunosupportive microenvironment[68]. Meanwhile, Routy *et al*[69] suggested that gut microbiota played a certain role in the resistance to anti-PD-1 therapy. Investigators discovered that, cancer cases who received anti-PD-1 therapy with antibiotics treatment had markedly reduced overall survival and PFS relative to those with no antibiotic treatment.

For investigating the association of antibiotic-induced dysbiosis with the reduced efficacy, investigators compared the compositions of gut microbiota in responders with those in non-responders[69]. Across the enriched bacterial species in the responders, *A. muciniphila* showed the highest correlation with the response rate of patients[69]. In addition, the IFN- γ production-induced immune reactions between Tc1 and *Enterococcus hirae* as well as between Th1/Tc1 and *Akkermansia muciniphila* predicted better patient survival[69]. In addition, clinical trial conducted using the mouse model suggested that mice that received FMT from responders showed superior response to the anti-PD-1 therapy and had higher proportion of CXCR3⁺CD4⁺TILs, whereas those that received FMT from non-responders, underwent antibiotic treatments and those in the GF status developed resistance to anti-PD-1 therapy[69]. Interestingly, antibiotic treatment reversed the efficacy of PD-1 blockade treatment through *A. muciniphila* recolonization in the presence or absence of *Enterococcus hirae*. Administration of *E. hirae* and *A. muciniphila* through oral gavage can increase CCR9⁺CXCR3⁺CD4⁺central memory T cells, promote IL-12 and IFN- γ secretion, and increase the CD4/Foxp3 ratio within tumour bed[69].

Role of gut commensals in the anti-CTLA-4 therapy

CTLA-4 is also a research hotspot apart from PD-1/PD-L1. The anti-CTLA-4 therapy can reverse the CTLA-4-hijacked activity of the co-stimulatory signal transduction pathway (CD28-CD80/86). Therefore, it is important to identify factors that modulate the anti-CTLA-4 therapy efficacy, so as to mitigate drug resistance and promote the treatment response.

Vétizou *et al*[70] carried out a trial for investigating the gut microbial impact on the efficacy of anti-CTLA-4 therapy[70]. In the mouse model of MCA205 sarcomas, compared with GF mice and those receiving broad-spectrum antibiotic treatment, specific pathogen-free mice showed higher efficacy in anti-CTLA-4 therapy[70], and commensal flora perturbation was observed after anti-CTLA-4 therapy. For certain species (*B. uniformis* and *Bacteroides thetaiotaomicron*), their abundances increased, while those of *Burkholderiales* and *Bacteroidales* declined[70]. Notably, *Bacteroides fragilis*, which was verified to be the immune-modulating bacteria, remained almost unchanged in the process of treatment[70,71]. Additionally, *B. thetaiotaomicron*, *Burkholderia cepacia*, and *B. fragilis* recolonization in GF mice or those receiving antibiotic treatment reversed the resistance to anti-CTLA-4 therapy[70]. Moreover, it was further detected that *B. fragilis* administered by oral gavage promoted DC maturation and elicited Th1 immune response within the tumour-draining lymph nodes[70]. Furthermore, adoptive Th1 cell transfer of cells specific to *B. fragilis* reversed the anti-CTLA-4 sensitivity in GF mice or those receiving antibiotic treatment to some extent[70]. In addition to the promoted anti-CTLA-4 effect, the treatment-related colitis was also alleviated by recolonizing *Burkholderia cepacia* and *B. fragilis* [70]. By FMT from melanoma cases, investigators discovered that the high abundance of *B. fragilis* was associated with tumour regression[70]. In addition, it was interesting to find that vancomycin treatment enhanced the ipilimumab efficacy, while alleviating side reactions that were not parallel to the promoted efficacy. To explore the reason, vancomycin might show indirect effect on promoting the abundance of *Bacteroidales* through suppressing *Clostridiales* proliferation[70].

Nonetheless, another trial examining the association of baseline gut microbiome with the clinical outcomes among the melanoma cases who developed metastasis came to different results from those obtained by Marie Vétizou[72]. Different from the results obtained from the clinical trial on mouse models, the low baseline abundances of *B. thetaiotaomicron* and *B. fragilis* but high abundance of *Bacteroides* were detected among the enrolled cases, which restricted the anticancer activity of CTLA-4. In addition, certain Firmicutes species, such as unclassified *Ruminococcus*, *Faecalibacterium* genus, *Clostridium XIVa*, *Lachnospiraceae* genus, *Gemmiger formicilis*, butyrate producing bacterium, and *Blautia* were associated with the increased response rates and superior clinical outcomes (prolonged overall survival and PFS). For exploring the underlying mechanisms, parameters associated with the immune status were analyzed, which suggested that cases exhibiting increased response to treatment had reduced baseline proportions of systemic proinflammatory cytokines (sCD25, IL-6, IL-8), CD4⁺/CD8⁺ T

cells, and Tregs while increased inducible T cell co-stimulator level in CD4⁺ T cells. Different from the above-mentioned clinical trials, antibiotic treatment made no difference to the composition of predominant microbiota or bacteria that potentially affected the efficacy[72]. It was previously suggested that antibiotic treatment reduced the efficacy of ICI treatment, and such findings should be further investigated. Such different results among different trials might be associated with certain factors such as the heterogeneities between human and mouse models and the bias in FMT.

Recently, Zhuo *et al*[73] assessed the protection of anti-CTLA-4 blocking Ab (CTLA-4 mAb) in combination with *Lactobacillus acidophilus* cell lysates in the syngeneic BALB/c mouse model with CRC. Compared with CTLA-4 mAb monotherapy, the body weight loss was mitigated by *L. acidophilus* lysates. Meanwhile, CRC growth was suppressed in mice receiving combined administration, suggesting the effect of lysates on enhancing the anticancer effect of CTLA-4 mAb detected using the mouse model [73]. Such improved therapeutic effect was related to the higher proportions of effector memory T cells (CD44⁺CD8⁺CD62L⁺) and CD8⁺ T cells, but the lower proportions of M2 macrophages (F4/80⁺CD206⁺) and Treg (CD4⁺CD25⁺Foxp3⁺) cells within TME[73]. Additionally, *L. acidophilus* lysates showed a certain immunomodulatory activity by inhibiting IL-10 expression in lipopolysaccharide-activated Raw264.7 macrophages and M2 polarization[73]. Finally, faecal microbiota was subjected to 16S ribosomal RNA gene sequencing, demonstrating that combined administration markedly suppressed the abnormally increased proteobacteria abundance and partially offset the CRC-caused dysbiosis among the model mice[73]. Consistently, Mager *et al*[74] isolated three bacterial species—*Bifidobacterium pseudolongum*, *Lactobacillus johnsonii*, and *Olsenella* species—that significantly enhanced the efficacy of anti-CTLA-4 treatment in CRC mouse models. Based on further research, intestinal *B. pseudolongum* improved immunotherapy response by producing the metabolite inosine. Decreased gut barrier function induced by immunotherapy enlarged systemic translocation of inosine and activated antitumour T cells. The effect of inosine relied on T cell expression of the adenosine A2A receptor as well as the required co-stimulation.

In general, alterations of intestinal bacteria exert a significant influence in ensuring the efficacy of cancer with ICIs treatments, with specific changes of the commensal microbes standing for a potential way that can be used to improve or to weaken ICIs efficacy. As a result, manipulating gut microbiota composition may provide a direct and effective method to strengthen the therapeutic effect of cancer ICIs.

FUTURE PROSPECTS OF FMT COMBINED WITH ICIS THERAPY IN CANCER TREATMENT

FMT refers to the process where the faecal suspension obtained from a normal subject is injected to the gastrointestinal tract of another subject for the sake of curing a certain disease. FMT is a direct and superior approach to enhance the efficacy of ICIs through modulating the gut microbiota in human beings. FMT has been adopted for more than 50 years. Faeces was initially adopted by Ge Hong in China in the 14th century to treat various conditions, such as diarrhea[75]. Eiseman *et al*[76] adopted faecal enemas to treat pseudomembranous colitis in 1958 [probably because of *Clostridium difficile* infection (CDI)], and this was also the first time to introduce FMT to the mainstream medicine. Thereafter, FMT has become more and more popular because of its simple use and effects on treating CDI. In recent years, FMT has been investigated in numerous other fields[77]. FMT has been found to be effective on certain disorders, like irritable bowel syndrome, inflammatory bowel disease, anorexia nervosa, metabolic disorders, multiple sclerosis, autoimmune disorders cancer, cardiovascular diseases, and neuropsychiatric disorders[78-82]. Similarly, FMT may represent an efficient approach to increase response rate in ICIs therapy. Currently, only a few clinical trials have studied the effects of FMT on PD-1 Ab immunotherapy response in cancer patients. Recently, Baruch *et al*[83] carried out one phase I trial for evaluating whether it was safe and feasible to perform FMT and re-induction of PD-1 blockage treatment among 10 melanoma cases who developed PD-1-refractory metastases (Table 2). Clinical responses were detected among 3 cases, including 2 with partial responses and 1 with complete response[83]. Obviously, treatment with FMT showed association with favorable changes in immune cell infiltrates and gene expression profiles in both the gut lamina propria and the TME[83]. Additionally, an ongoing single-center phase 2 clinical trial (NCT03341143) investigates the therapeutic effect of FMT combined with pembrolizumab on melanoma patients who develop resistance to the anti-PD-1 treatment[84]. However, results are not reported at present. In

conclusion, such preliminary results shed more lights on the effect of FMT on anticancer treatment. As a result, FMT combined with ICIs has been regarded as the potential anticancer treatment.

CONCLUSION

Accumulating evidence has demonstrated the shift in gut microbiome composition influencing ICIs efficacy. Nevertheless, it obviously shows that in-depth studies on the mechanism(s) of interaction between gut microbiota and ICI efficacy need to be performed in different cancer populations. Additionally, FMT combined with ICIs may serve as a new anticancer treatment that requires more investigation. Scientific research in this field is just at the beginning stage, and more relevant information is needed. To this end, first of all, it is of great importance to determine the mechanism by which FMT re-establishes the balanced gut microbiota, finally achieving the remarkable cure rate among cancer cases who receive ICI therapy. Secondly, well-designed randomized controlled trials are required to ensure the safety and efficacy of FMT for cancer patients with ICIs treatment. Besides, additional high-quality data (e.g., longitudinal study) are also necessary to explore potential adverse effects. Moreover, it is of importance to study the composition of the small intestinal and faecal microbiota before and after FMT. These studies can contribute to better understanding the mechanisms of this therapy as well as identify microbes and their products involved in the pathogenesis of cancer. Thirdly, the best gut microbiota composition to enhance ICIs efficiency need to be recognized. On this basis, it is important to choose the right donors. Finally, FMT represents a relatively simple procedure during short duration. Compared with the repeated hospitalization and conventional therapy, FMT has low costs. Thus, the most appropriate method and duration for FMT needs to be determined. For this reason, besides conventional approaches, FMT is promising as an alternative therapy for cancer in the future.

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