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Review article

The role of intestinal flora on tumor immunotherapy: recent progress and treatment implications

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A B S T R A C T

Immunotherapy, specifically immune checkpoint inhibitors, has emerged as a promising approach for treating malignant tumors. The gut, housing approximately 70 % of the body's immune cells, is abundantly populated with gut bacteria that actively interact with the host's immune system. Different bacterial species within the intestinal flora are in a delicate equilibrium and mutually regulate each other. However, when this balance is disrupted, pathogenic microorganisms can dominate, adversely affecting the host's metabolism and immunity, ultimately promoting the development of disease. Emerging researches highlight the potential of interventions such as fecal microflora transplantation (FMT) to improve antitumor immune response and reduce the toxicity of immunotherapy. These remarkable findings suggest the major role of intestinal flora in the development of cancer immunotherapy and led us to the hypothesis that intestinal flora transplantation may be a new breakthrough in modifying immunotherapy side effects.

1. Introduction

Over the past 20 years, the advent of immunotherapy has revolutionized cancer treatment. Immunotherapy improves the ability of a patient's immune system to detect and eradicate cancer cells. Tumor immunotherapy includes drugs that enhance specific components of the immune response, enabling them to directly target and eliminate cancer cells or reinforce the overall function of the immune system [1]. Furthermore, the field of cancer immunology is on the verge of introducing sophisticated combinational treatments that have the potential to improve clinical responses and ultimately cure cancer [2]. To date, however, malignancy has been a major threat to global health, affecting people worldwide.

Human intestinal flora colonization begins at birth and is completed around age 3. It comprises over 1000 species, making it the largest microbiome in the human body. Intestinal flora co-exists with the host and constitutes an important micro-ecosystem, substantially impacting human immune regulation and digestion, being involved in bioantagonism, and possessing antitumor activities [3–5].

Intestinal flora impacts the efficacy of immunotherapy and its adverse effects. Additionally, the composition of gut microbiota is also involved in the occurrence of some types of cancer. Although only a small percentage of microbes directly cause cancer, many

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contribute to the growth of cancer through the modulation of the immune system [6]. For example, *Helicobacter pylori (H. pylori)* degrades p53 protein in gastric epithelial cells, leading to gastric cancer. CagA protein secreted by *H. pylori* interacts with E-calmucin in the gastric epithelium, promoting rapid cell proliferation and increasing the risk of epithelial cancer [7]. Other bacteria that secrete virulence factors exhibit similar carcinogenic effects [8,9]. Additionally, bacteria like *Shigella fowleri* and *Bacteroides fragilis (B. fragilis)* can induce DNA damage and genomic mutations by interfering with the DNA damage response or producing oxidative stress [10,11]. In contrast, some bacteria in the gut also maintain immunity to the intestinal mucosa. *B. fragilis* can induce naïve $CD4^+$ T cells to differentiate into regulatory T cells (Treg cells) that secrete large amounts of anti-inflammatory cytokines such as IL-10 [12]. A recent study revealed for the first time that *Lactobacillus reuteri (L. reuteri)* can translocate to melanoma in order to increase the therapeutic efficacy of immune checkpoint inhibitors as well as the molecular mechanisms by which it functions. In this study, the authors' research team demonstrated that the catabolic metabolite of dietary tryptophan, indole-3-carboxaldehyde (I3A), produced by *L. reuteri*, induces CREB activity dependent on the aryl hydrocarbon receptor (AhR)-, which in turn directs the effector function of Tc1 (an IFN-γ-producing $CD8^+$ T-cell) in order to enhance the antitumor effect of immune checkpoint inhibitors (ICIs) [13].The intestinal flora plays a complex role in regulating systemic tumor immunity. Consequently, gut microbes influence tumorigenesis, cancer development, and the response to treatment, particularly to immunotherapy, a major scientific breakthrough in cancer treatment [14].

A review of new advances in the study of mechanisms in the influence of intestinal flora on immunotherapy may bring us new thoughts and a more comprehensive consideration of this relationship. The aim of this review was to investigate the increasing volume of research concerning the gut microbiota as a regulator of the effects of tumour immunotherapies.

2. The interaction between intestinal flora and host immunity

2.1. Intestinal flora directly affects immunity

The gut microbiome, which refers to the collection of microorganisms residing in the human gastrointestinal tract, functions separately from the host's immune system. While the gut microbiome interacts with the immune system and influences immune responses, it operates as a distinct entity. The flora of the intestine plays an important role in the body's immunity. The intestinal cells are safeguarded by the mucus layer in the intestine. Research has indicated that the colonic epithelium of humans, rats, and mice is mainly characterized by elevated levels of a secreted mucin called MUC2 [15,16]. Insufficient levels of MUC2 result in colon inflammation and contribute to the emergence and persistence of experimental colitis [16,17]. Simultaneously, the intestinal mucus layer facilitates the thriving of the intestinal flora within the confines of the intestine [18]. With approximately 100 trillion bacteria, the human gastrointestinal tract serves as the main site for microbial interaction with the host immune system [19,20]. The intestinal epithelium consists of a monolayer of various intestinal epithelial cells (IECs), which are involved in innate immunity [21](Fig. 1).

We should be cognizant of the fact that intestinal flora is vulnerable to other elements when carrying out experiments concerning

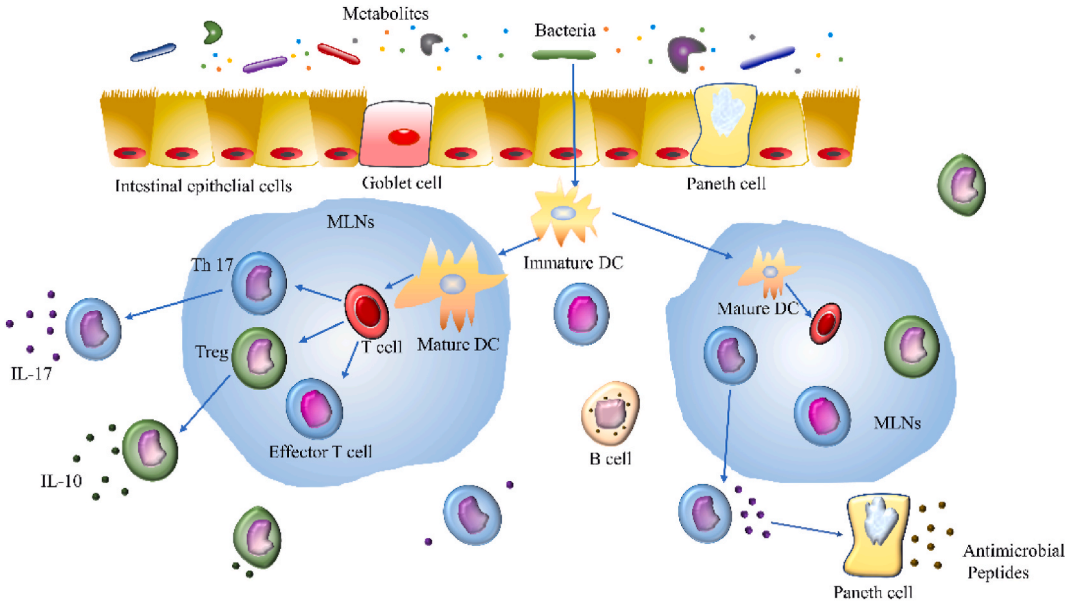

Fig. 1. Mucosal immunity to pathogenic intestinal bacteria.
The intestinal mucosa is a single-cell layer composed of intestinal epithelial cells (IECs) and intraepithelial lymphocytes, with cupped cells and Paneth cells located between the IECs. Bacteria and bacterial metabolites can activate immature dendritic cells (DCs) through the intestinal mucosa, allowing DCs to mature and migrate to the mesenteric lymph nodes (MLNs). In the MLNs, mature DCs can activate T cells, causing them to differentiate into effector T cells, regulatory T cells (Tregs), or Th17. Tregs secrete anti-inflammatory interleukin (IL)-10. Th17 cells secrete IL-17, which induces the production of antimicrobial peptides by Paneth cells.

intestinal flora. Research has demonstrated a strong correlation between dietary habits and gut flora. The study has revealed that the intake of Myrciaria dubia modifies the gut microbiota, amplifies its anti-tumor properties, and modifies the anti-PD-1 reaction. Myrciaria dubia contains a significant amount of Castalagin, which has been identified as the primary bioactive compound responsible for its antitumor properties [22]. In addition, Food plays a crucial role in the metabolism of the gut microbiome, affecting its structure and balance, as well as changing the release of its metabolites [23,24].As an illustration, a ketogenic diet has the potential to hinder bowel cancer by stimulating bacterial synthesis of beta-hydroxybutyrate [25]. Furthermore, a study conducted by a group of scientists affirms that the consumption of antibiotics can induce disruptions in the gut microbiota, resulting in an inflammatory reaction and a decline in the body's immune response [26].

Bacteria, including subdominant bacteria such as those belonging to *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*, as well as other microorganisms, make up more than 90% of the intestinal flora [27]. Furthermore, the gastrointestinal tract contains approximately 70% of the body's lymphocytes and serves as the largest immune organ [28]. The interaction between intestinal flora and the immune system of the intestinal mucosa is a key factor in maintaining mucosal homeostasis.

The interaction between the gut microbiome and host immunity begins at birth, as the microbiome contributes to the development of immunity. Subsequently, the immune system coordinates with components of the gut microbiota [29,30]. Although the mechanisms by which the intestinal flora regulates immune homeostasis have not yet been investigated, certain studies have demonstrated that specific bacterial strains can modify the immune response by influencing the development of specific lymphocyte subtypes [21].

Furthermore, the influence of gut bacteria extends beyond the gut itself, affecting immune mechanisms throughout the body. First, small molecules produced by gut bacteria can circulate in the bloodstream, influencing immune responses in distant organs. Thus, the bidirectional connection between the gut and brain known as the gut-brain axis is commonly observed in patients suffering from neurodegenerative diseases (e.g., Parkinson's disease or multiple sclerosis) in which alterations in the gut microbiota are observed [31–33]. In the gut, bacteria have been shown to be able to convert the amino acid tyrosine, which is commonly present in the diet, into 4-ethylphenyl sulfate (4EPS), which crosses the blood-brain barrier and reduces the maturation of oligodendrocytes of neurons that make up myelin in the brain, which contributes to the development of anxiety [34]. These studies help to elucidate the molecular mechanisms by which the recently observed changes in the gut microbiota are associated with complex affective behaviors. Second, the mucosal tissues found throughout the body, which are influenced by the gut microbiota, possess a shared immune system specialized for mucosal protection. For example, certain bacterial products, such as lipopolysaccharide (LPS) and peptides, can stimulate mucus secretion from the mucosa and restore the properties of mucus [35]. Finally, gut bacteria regulate the development of immune cells throughout the body [36]. Innate lymphoid cells (ILCs) are a recently discovered group of intrinsic immune cells that form the first line of defence of the immune system in conjunction with the skin and mucosal membranes by either direct action or the indirect secretion of immune factors. They often interact with microorganisms in the gut or alter the microenvironment in order to maintain body homeostasis. One of these, ILC3, is an important molecule for the regulation of TH17, which may interact with microorganisms and T cells via the production of immune factors (e.g., IL-17, IL-22, etc.) [37]. Gut microbes are important regulators of the tumor microenvironment (TME) [38–42]. Consequently, a gut microbiome containing a higher percentage of beneficial bacteria contributes to a more robust immune system and enhanced adaptability to the external environment [36]. In conclusion, the intestinal flora exerts a profound and systemic impact on the body's immunity.

2.2. *Intestinal flora affects host immunity through its metabolites*

Gut microbiota not only directly regulates the immune function, but also through its metabolites which affect the expression of host immune-related genes. Metabolites of intestinal flora can enter the cells of the host and regulate their function, being involved in the maintenance of intestinal integrity, inhibition of inflammation, and host tumor suppression and immunomodulation [43,44]. For example, intestinal flora stimulates directly or through its metabolites plasma cells to produce IgA and Paneth cells to secrete antimicrobial peptides which promote the maturation and migration of local dendritic cells to the lymphatic region. Subsequently, this activates effector T cells, regulates T and Th17 cells, and induces immune responses [45,46]. The identification of *Akkermansia muciniphila*, a microorganism associated with a homologous adaptive immune response in the intestinal flora, confirms that metabolites secreted by the intestinal flora regulate the body's homeostasis [47]. Additionally, microbial metabolites can induce innate immune memory in immune cells [48]. Other small molecules in the gut may also impact immunity. For example, in the steady-state, small intestine goblet cells (GCs) function as passages delivering low molecular weight soluble antigens from the intestinal lumen to underlying CD103+ lamina propria (LP) - dendritic cells (DCs). The preferential delivery of antigens to DCs with tolerogenic properties implies a key role for this GC function in intestinal immune homeostasis [49]. Furthermore, the production of pro-inflammatory interleukin (IL)-17 by effector T helper cells (Th17) in the gut requires signals from intestinal bacteria to balance with the production of Foxp3C Tregs [50].

During tumor immunotherapy, normal or pathological immune responses can occur [51]. Butyric acid enhances the tumor-suppressive effects of cancer immunotherapy. Other microbial metabolites can interact with the host's immune system to balance and counteract various disease states. For example, butyrate, a metabolite of bacteria, can enhance the tumour suppressive effect of an immunogenic anti-cancer therapy [52]. Furthermore, metabolites of the intestinal flora such as butyric acid and pyridoxine (vitamin B6) can induce apoptosis in cancer cells, and these apoptosis products are further identified and activated by immune cells to trigger an anti-tumor immune response and bolster the body's immunity [53].

Intestinal flora and its metabolites have an important impact on intestinal immunity as well as that of the entire body. Maintaining a healthy gut immune function relies on the presence of normal intestinal flora.

2.3. Cancer immunotherapy and intestinal flora

Immunotherapy is a game-changer in oncology treatment and has induced sustained clinical responses in various types of cancer [54–59]. It encompasses various approaches such as oncolytic virus (Ovs), cancer vaccines, cytokine therapies, adoptive cell transfer (ACT), or administration of immune checkpoint inhibitors (ICIs) [60]. OVs control the functioning of immune checkpoints in the TME primarily through their role as genetic carriers for specific checkpoint antibodies, as well as their oncolysis and secretion of cytokines and chemokines, which work together with immune checkpoint inhibition [61]. In recent years, due to the development of genetic engineering and virus transformation technology, oncolytic virus therapy has made significant advancements. *Talimogene laherparepvec* has been approved for the treatment of unresectable metastatic melanoma [62]. Studies have demonstrated a strong association between lysosomal virus and immune checkpoint blockade therapies [63,64]. For example, in order to enhance the efficacy of antibodies that impede PD-1/PD-L1- or CTLA4/B7-mediated immune suppression, $CD8^+$ T cells and NK cells necessitate oncolytic viruses-mediated immune activation, involving selective viral replication and targeted induction of antitumor immune responses in the TME [65]. Research into the connection between intestinal flora and lysosomal viral therapy is limited. In recent times, there has been a proposal for the utilization of bacterial-assisted OVs that specifically target tumors, aiming to bind liposome-encapsulated OAs to tumor-homing *Escherichia coli* BL21 (E. coli-lipo-OAs) in order to enhance the effectiveness of tumor immunotherapy [66]. Notably, the efficacy of E. coli-lipo-OAs administered through self-driven bacterial microbial vectors was amplified by over 170 times in comparison to intravenous bare OAs in non-small cell lung cancer [66]. Cancer vaccines utilize tumor-specific antigens to trigger T-cell-mediated antitumor immune responses, and early studies confirm their potential as immunotherapies for tumor treatment [67–69]. The gut microbiome plays an important role in the formation of the immune system through the presence of Peyer's patches (PPs), plasma cells, and lymphocytes in the gut-associated lymphoid tissue [70]. It is widely acknowledged that the gut microbiota has a strong correlation with the body's immune system. Therefore, the role of intestinal flora variability in tumor vaccine efficacy deserves in-depth study.

Cytokines are released by both immune and non-immune cells in response to cellular stress, such as infection, inflammation, and tumorigenesis [71]. Interleukin 2(IL-2) and interferon-alpha (IFN-α) are two of the most commonly used therapeutic cytokines in cancer treatment. The IL-2 cytokine is essential for the proper functioning of both the adaptive and innate immune systems, and is a major factor in the growth, resilience, and transformation of T cells. Furthermore, it stops T cell responses to maintain self-tolerance, as well as act as a growth factor for $CD4^+$ T cells and natural killer (NK) cells, and contributes to the production of antibodies by B cells [71–73]. The utilization of substantial amounts of IL-2 in clinical settings, as a representative illustration of cytokine therapies, may result in the regression of cancer in patients suffering from metastatic cancer [74,75]. The study suggests that low-dose IL-2 (IL-2LD) has a positive impact on the gut microbiota, thereby enhancing the primary effect of IL-2LD on the equilibrium of Treg/effector T cells [76]. It is noteworthy that Tregs are capable of affecting gut microbiota, and it is acknowledged that IL-2LD has a direct effect on Tregs [77]. Therefore, we can hypothesize that IL-2 may have an effect on gut microbiota by altering Tregs. Interferons (IFNs) encompass a wide range of cytokines, playing a crucial role in determining the effectiveness of antitumor immunity [78]. Research has demonstrated that the combination of gut bacteria and interferon can improve the effectiveness of immunotherapy [79,80]. By co-colonizing eleven bacterial strains from healthy human feces in the intestine, the production of IFN-γ-producing CD8 T cells in the mouse intestine and other organs was effectively induced, leading to improved IFN-γ+ CD8 T-cell-mediated anti-tumor immunity, inhibition of tumor progression in mice, and enhanced therapeutic efficacy of immune checkpoint inhibitors without causing colitis as a side effect [81]. Their use in clinical practice is limited due to their low tolerability and substantial toxicity [60]. However, combining them with other immunotherapies may overcome these limitations.

ACT is an immunotherapy approach that involves genetically engineering autologous cells, amplifying them in vitro, and then injecting them into a patient to target cancer cells [82–84]. ACT has shown promising results since its experimental stages in the 1980s and has further improved, possessing increased efficacy [75,85,86]. One specific type of ACT, CAR-T immunotherapy, modifies T cells through genetic engineering to enhance their antitumor capabilities [87,88].

Immunotherapy has made substantial breakthroughs in hematologic malignancies, with the approval of CAR-T cell therapy products, Kymriah and Yescarta, by the U.S. Food and Drug Administration (FDA) in 2017 [83,89,90]. Immune checkpoints are molecules that suppress signaling pathways. They are used by cancer cells to evade immune surveillance. ICIs enhance antitumor immune responses by blocking co-inhibitory signaling pathways, leading to immune-mediated clearance of tumor cells [91–94]. ICIs have revolutionized cancer treatment as first-line agents for a wide range of solid and liquid tumors. Tumor immunotherapy holds promise as a crucial tool for future tumor treatment. However, the challenge lies in inducing an immune response in tumors that undermine autoantigen immunity. Strategies such as sequential migration of immune effector factors, vaccination, and immunomodulatory therapy are required to address this issue [95].

The human gut contains an impressive 3.3 million unique genes, which is 150 times larger than the human genome. Diversity analysis indicates the presence of approximately 1000 bacterial species in our gut [96]. The composition of intestinal flora differs among individuals and is influenced by various factors. However, the diversity and abundance of different gut bacteria ultimately maintain a dynamic balance.

Intestinal dysbiosis, characterized by imbalances in gut microbial communities, has been associated with several diseases, including inflammatory bowel diseases, obesity, and type II diabetes.

Gut microecology is closely associated with cancer progression. Furthermore, the intestinal microecology of patients with colorectal cancer is significantly different from that of healthy individuals [97]. The abundance of cancer-promoting bacteria increases, while that of beneficial bacteria decreases in the gut of patients with colon cancer [98]. Moreover, *Clostridium perfringens* (*C. perfringens*) , located in the intestines of humans and animals, suppresses antitumor immunity by inhibiting the tumor cell-killing

capacity of NK cells [99,100]. Neutrophils, crucial cells in cancer progression, can influence and promote metastasis of cancer cells. Intestinal flora reduces the circulation of neutrophils in the blood, thereby impacting tumor progression [101–104]. The findings indicate that sodium butyrate, a byproduct of *R. intestinalis,* safeguards neutrophils against the generation of neutrophil extracellular traps (NETs) induced by lipopolysaccharide (LPS) or tumor necrosis factor-α (TNF-α), with NOX2 potentially playing a significant part [105]. Moreover, the presence of sodium butyrate resulted in a substantial reduction in the expression of NADPH oxidase 2 (NOX2) in neutrophils stimulated by LPS or TNF-α [105]. An analysis of the number of neutrophils in mice with a healthy gut microbiota revealed that the gut microbiota can alter neutrophils post-birth and affect the host's immunity to infection [106–108]. Additionally, tumor growth is directly promoted by certain products of the gut microbiome, such as those which induce cancer-causing mutations in the host [109].

A significant proportion of patients do not benefit from immunotherapy, because of the heterogeneity of this therapeutic approach. Factors such as patient characteristics, clinical trial design, and drug interactions can also influence treatment response rates. To screen appropriate patients and improve efficacy, it is essential to predict treatment responsiveness and understand the causes of heterogeneity in effectiveness.

Certain gut microbes have been associated with enhanced efficacy of ICIs [110,111]. The experiments involving mice receiving microbial transplants of human flora revealed the efficacy of CTLA-4 blockers in treating melanoma patients, along with the antitumor properties of the byproducts derived from *Mycobacterium fragilis* [110]. These properties contributed to the fight against cancer through the use of anti-CTLA-4 inhibitors [110]. These studies demonstrate the significant contribution of bacteria to the effectiveness of CTLA-4 inhibitors [110]. Recently, it has been shown that *Bifidobacterium bifidum (B. bifidum)* mediates innate immunity to enhance the efficacy of anti-PD-1 monoclonal antibodies in a mouse model of melanoma, and that *B. bifidum* also attenuates irAEs induced by CTLA-4 blockade; thus, the question of whether *B. bifidum* can simultaneously enhance efficacy and reduce toxicity of PD-1/PD-L1 blockade as well as CTLA-4 blockade continues to be explored [112]. Using gut microbes might be a strategy to improve the effectiveness of immunotherapy. Therefore, the standardized incorporation of gut microbes into immunotherapy protocols should be considered. The gut microbiome interacts with the host, influencing the state of the host's gut immune system and promoting and regulating both natural and adaptive immunity [113]. Consequently, the intestinal flora plays a crucial role in tumorigenesis and cancer progression.

2.4. FMT affects immune checkpoint-blocking therapy

2.4.1. Effect of fecal bacterial transplantation on the mechanism of immune checkpoint inhibitors

Further studies have confirmed that intestinal flora influences immunity and the effect of ICIs through multiple mechanisms

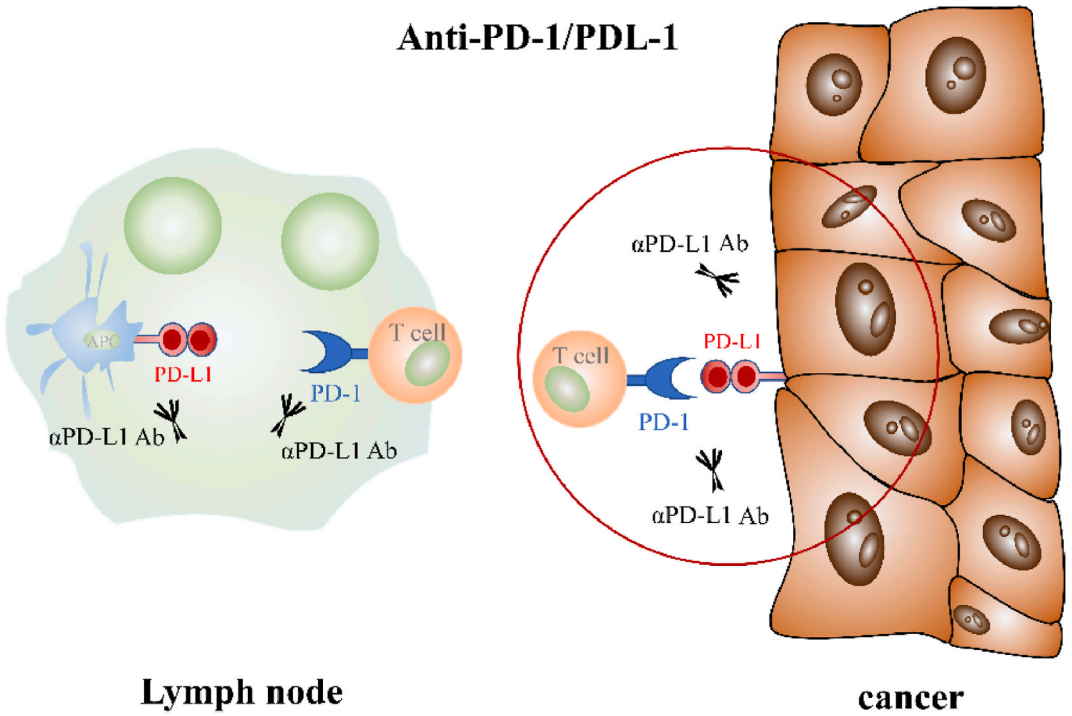

Fig. 2. Programmed cell death protein 1 (PD-1)/Programmed cell death-ligand 1 (PD-L1) and tumor cell immune escape.
Some tumor cells actively suppress T cells by expressing inhibitory molecules like PD-L1, which binds to the PD1 receptor on T cells and inactivates them; administration of antibodies against PD-1 and PD-L1 allows T cells to be activated and destroy cancer cells.

[114–119]. Therapy with ICIs inhibits immune checkpoints, restores T-cell activity, and enhances the response of the immune system to tumor antigens [94]. Furthermore, the efficacy of ICIs is closely associated with the gut microbiota [110,111]. Recent research has suggested that FMT may enhance the antitumor properties of ICI and combat immunotherapy resistance [118–120]. In a clinical trial involving 10 melanoma patients who were not responding to PD-1 blockade and were administered FMT followed by re-induced anti-PD-1 therapy, it was observed that 3 out of the 10 patients experienced a decrease in tumor size, resulting in 2 instances of partial remission and 1 case of complete remission [121]. Currently, the most extensively studied molecules in immunotherapy are anti-programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte–associated antigen (CTLA)-4 antibodies [122–125]. Antigen-specific T cells play a key role in eliminating tumor cells [126]. PD-1 is a type I transmembrane protein expressed primarily in immune cells, while PD-L1 is a member of the B7 family of antigen-presenting co-stimulatory/co-inhibitory molecules expressed by various cell types, including cancer cells [127]. The release of tumor antigens from tumor cells triggers the cancer-immune cycle. Antigen-specific T cells recognize these tumor antigens presented by APCs through major histocompatibility complexes and subsequently undergo activation; after activation and proliferation, T cells migrate to specific sites guided by chemokine gradients [128,129]. To regulate the activity of T cells and prevent their excessive activation, immune checkpoints such as PD-1 and its ligand PD-L1 are engaged [128,129]. However, studies have revealed that activation of the PD-1/PD-L1 pathway contributes to tumor immune evasion [130]. When PD-L1 and PD-L2 bind to PD-1 on the surface of T cells, they inhibit their activity and induce apoptosis of tumor-specific T cells (Fig. 2) [131]. Inhibiting the interaction between PD-L1 and PD-1 can prevent the inactivation of T cells. Some cancers have shown resistance to treatment with anti-PD1/PDL1 antibodies. This may be due to the fact that anti-PD-1/PD-L1 antibodies only partially overcome inhibitory signals in the TME, as there may be additional inhibitory pathways impeding T cell function [132].

Furthermore, the level of expression of PD-1 in T cells influences the efficacy of anti-PD-1 therapy, with a higher level of expression of PD-1 associated with poorer treatment response [133]. T cells produce interferon-γ (IFN-γ), which acts on its receptors to activate Janus kinase (JAK1/2) and trigger signal transduction and transcriptional activation. This leads to the expression of genes stimulated by INF-γ and plays a role in tumor antigen recognition [134,135]. Increased expression of CD274 (encoding PD-L1) results in the inactivation of tumor-specific T cells [136].

The CTLA-4 functions as an inhibitory signal, impeding T-cell activation through multiple mechanisms. Thus, it is important for the termination of immune responses [137–139]. CTLA-4 expression is regulated by various factors, including microRNAs (miRNAs), the nuclear factor of activated T cells, and the transcriptional regulator Foxp3, all of which play roles in controlling CTLA-4 surface expression or gene induction in lymphocytes [140–142].

A recurrent CTLA4-CD28 fusion, comprising the extracellular and transmembrane regions of CTLA4 and the intracellular region of CD28, has been identified in T-cell lymphoma or advanced Sezary syndrome. This fusion is significantly elevated and serves as a potential target for anti-CTLA-4 cancer immunotherapy [143–145]. CTLA-4 and CD28 have different levels of expression and transport profiles. Co-stimulation of CD28 promotes T-cell survival by upregulating the expression of Bclxl and inducing IL-2 mRNA to promote T-cell proliferation [146,147]. Conversely, CTLA-4 inhibits signaling, terminates T-cell responses, and competes with CD28 for binding to the T-cell co-ligand, thereby dampening the survival and proliferation of T cells [148,149]. CTLA-4 exerts inhibition through multiple mechanisms, including suppression of T-cell proliferation, cell cycle progression, IL-2 production, and T-cell differentiation [150,151]. Additionally, CTLA-4 plays a role in preventing autoimmunity by inhibiting the differentiation of Th17 and promoting the differentiation of Treg cells, thus regulating the balance between auto-reactive T cells and Tregs [152]. The regulatory mechanisms of CLTA-4 are closely related to tumor treatment, as overexpression of both PD-L1 and CTLA-4 are significant suppressors of antitumor immunity. There are regulatory similarities between PD-L1 and CTLA-4, and drugs that mutually modulate them could possess enhanced therapeutic efficacy.

FMT is the process of transferring beneficial fecal bacteria from healthy individuals to patients with various diseases, restoring the normal composition and function of the intestinal flora [153]. Currently, the gut microbiome is known to be strongly associated with cancer [45,116,154]. Specific fecal bacteria can promote colon cancer [155]. For example, anaerobic digestive *streptococci* can attach to the surface receptors of the host's IECs, activating oncogenic signaling cascades in the colonic cells [155], triggering a pro-inflammatory immune microenvironment favorable for colorectal cancer growth, and suppressing antitumor immunity [155]. *C. perfringens*, a prominent bacterium, promotes the development and progression of colorectal cancer by activating a pro-cancer molecular pathway, the calmodulin E/β-linked protein signaling pathway. This is mediated by the activation of the FadA receptor on IECs [156]. Additionally, *C. perfringens* enhances resistance to chemotherapy by modulating autophagic lysosomes [157]. Another bacterium, *B. fragilis,* produces specific toxins and promotes colorectal cancer by disrupting the regulation of specific small RNAs [158]. The intestinal microbiota plays a crucial role in immune homeostasis and tumorigenesis [154,159].

Sivan et al. [111] hypothesized that the composition of symbiotic bacteria could influence the response rate to immunotherapy. They conducted experiments with mice, manipulating the microbial populations by specific feeding and performing FTM. Thus, they examined the effects of microbial composition on the response to the therapy with ICIs. In the first published prospective study of human gut microbiota and ICIs, Frankel et al. [160] demonstrated that similar treatments had different efficacies in different patients with melanoma and distinct gut microbiota. Routy et al. [120] conducted a cohort study that included 249 tumor patients treated with anti-PD-1/PD-L1 antibodies and found that antibiotic administration was an independent risk factor for primary resistance to ICIs. Heshiki et al. [161] revealed that the characteristics of the intestinal flora were independent of the type of cancer. Perez-Chacona et al. analyzed that the efficacy of CTLA-4 blockade against tumors was contingent upon the presence of Bacteriodes species like *B. thetaiotaomicron* and *B. fragilis*, as well as the proteobacteria *Burkholderia cepacia*, in the intestinal microbiota [162]. The occurrence of these bacterial species was heightened in patients who received anti-CTLA-4 treatment [162]. The malfunctioning reaction to anti-CTLA-4 in GF mice could be remedied through gavage with the aforementioned three species, by introducing the microbiota of

patients treated with anti-CTLA-4 and enriched with the *Bacteriodes*. By immunizing with *B. fragilis* polysaccharides and transferring the *B. fragilis*-specific Th-1 cells generated in conventional mice through the anti-CTLA-4 treatment, a positive response was observed [162]. Despite the abundance of clinical data, the precise ways in which gut bacteria stimulate anti-tumor immunity remain unclear. In a recent study, it was discovered that the gut microbiome reduces the expression of PD-L2 and its binding partner, repulsive guidance molecule b (RGMb), in order to enhance anti-tumor immunity and pinpoint bacterial species responsible for this phenomenon.PD-L1 and PD-L2 have PD-1 as their binding partner, however, PD-L2 can also attach to RGMb [163]. Reserch's findings indicate that inhibiting the interactions between PD-L2 and RGMb can effectively overcome resistance to PD-1 pathway inhibitors, which is influenced by the microbiome [163]. The combination of antibody-mediated blockade of the PD-L2–RGMb pathway or conditional deletion of RGMb in T cells, along with an anti-PD-1 or anti-PD-L1 antibody, induces anti-tumour responses in various mouse tumour models that do not exhibit a response solely to anti-PD-1 or anti-PD-L1 (germ-free mice, antibiotic-treated mice, and even mice colonized with stool samples from an unresponsive patient) [163]. The PD-L2–RGMb pathway is downregulated in these studies, which is a mechanism through which the gut microbiota can enhance responses to PD-1 checkpoint blockade [163]. The findings additionally establish a potentially efficacious immunological approach for managing patients unresponsive to PD-1 cancer immunotherapy.

2.4.2. The impact of FMT on immune-related adverse reactions (irAEs)

Immunotherapy may cause severe irAEs in some patients [164]. One of the most common types of such irAEs is ICI-associated colitis, a condition very similar to autoimmune colitis [165,166]. However, in-depth research in this area is lacking. Furthermore, the mechanisms by which gut microbes influence antitumor immunity have not been fully explained. Future studies will need to include larger sample sizes and conduct more comprehensive microbial analyses to elucidate specific mechanisms and guide clinical decision-making.

However, the clinical use of immunotherapy has brought forth irAEs [167]. Thus, three-quarters of patients receiving ICIs may experience irAEs [120]. Certain ICIs, such as anti-PD-1 antibodies, can lead to adverse gastrointestinal events [168]. Generally, inhibition of the CTLA-4 pathway leads to higher levels of irAEs than that of the PD-1/PD-L1 pathway. Additionally, anti-PD-L1 antibodies are less toxic than PD-1 antibodies [169,170]. Furthermore, certain combinations of drugs may result in more severe complications than using monotherapy [171]. It is important to note that a substantial proportion of patients with cancer either show resistance to therapy with ICIs or only experience transient responses due to heterogeneity [172].

Colitis is one of the most common irAE of therapy with ICIs. The standard treatment for ICI-associated colitis involves immunosuppressive therapies including corticosteroids and/or drugs targeting tumor necrosis factor-alpha (TNF-α). However, all of them have significant adverse effects [173]. In two patients with refractory ICI-associated colitis, add-on therapy consisting of one or two FMTs, respectively, resulted in symptomatic remission of the colitis. The patients had a significant reduction in $CD8^+$ cytotoxic T cells in the colonic mucosa and an increase/retention of CD4+FoxP3+ T cells, which could be a potential mechanism for underlying the effectiveness of FMT [173]. Therefore, FMT may be an effective treatment for refractory ICI-associated colitis. Thus, FMT ameliorates the adverse effects of immune checkpoint-blocking therapy. Nevertheless, the number of relevant studies is limited, the study cohort is small, and further research is needed to overcome these limitations.

The development of irAEs may be associated with the presence of autoreactive T cells, decreased immune tolerance, molecular mimicry, and antigen dissemination. Differences in individual intestinal flora are also associated with the development of irAEs; however, the underlying mechanism is unclear [174,175]. FMT has been shown to influence the therapeutic effect of cancer therapy in two ways: first, it can directly impact the efficacy of anticancer immunotherapy by modifying intestinal microbiota and improving the metabolism of bile acids [176]. Second, FMT can be effective in treating refractory CPI-associated colitis by increasing the abundance of beneficial bacteria and reducing that of pathogens [173]. Additionally, FMT is a key technique for treating *recurrent C. difficile* infections [177]. However, the safety of FMT remains controversial, with some studies reporting mild adverse reactions such as mild fever, constipation, and diarrhea. Serious adverse effects including infection, sepsis, pneumonia, and endoscopic complications are relatively rare [178–180]. The efficacy of FMT requires further validation through large-scale multicenter clinical studies.

2.5. Clinical evidence of intestinal flora affecting therapy with ICIs

The impact of gut microbiota on treatment response has been demonstrated in preclinical models and various human populations [118–120,160,181,182]. Currently, the FDA has approved for clinical use two types of ICIs: antibodies against PD-1, PD-L1, or CTLA-4 [183]. These anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies are widely used [184–186].

Clinical trials with anti-PD-1 antibodies have shown promising antitumor activity and improved overall patient survival rates in patients with melanoma [187–190]. However, due to intra-individual variability, some patients still require combination therapy to achieve significant results [191]. Patients with non-small cell lung cancer who received antibiotics one month before or after their first PD-1 injection exhibited shorter progression-free survival (PFS) ($p < 0.0001$) and overall survival (OS) ($p = 0.0021$), compared to patients who did not receive antibiotics [192]. This might be due to the effect of antibiotics on gut microbiota. For patients with lung cancer receiving Nivolumab, a more diverse gut microbiome is associated with improved immunotherapeutic effects [193]. Bacteria such as *Bifidobacterium longum* and *Prevotella copri* have been associated with enhanced immune response [193].

Therefore, the composition of the host gut microbiota is a major determinant of the response to ICIs and may emerge as a factor to be considered in future ICIs-based therapeutical protocols [110,118,119,160].

The results of microbial studies differ among researchers from different geographical regions, indicating that geographical factors may influence immunity [193]. A genomic map of human gut bacteria suggests that the composition of gut bacteria varies globally

[194]. Furthermore, the gut microbiome is increasingly recognized as an essential component of cancer immunotherapy [195]. Intestinal flora can be used as an adjunct to therapy with ICIs, reducing their side effects and improving treatment outcomes [111]. Therefore, region-specific immunotherapy protocols with ICIs should be developed based on the composition of the intestinal flora of patients (Table 1). Further research is needed in this area, and clinical trials are being currently conducted.

3. Conclusions

Ongoing clinical trials in tumor immunotherapy hold the potential to revolutionize cancer treatment. Emerging evidence suggests that treating cancer by using gut bacteria to activate the host's immune system offers advantages over traditional approaches. Molecular-targeted immunotherapies, such as PD-1/PD-L1 inhibitors, are being investigated and show promise for future tumor treatments. Although anti-PD1/PDL1 therapies have been shown to be effective in treating solid tumors, only a small percentage of patients experience durable sensitization. Patients who initially react positively to treatment may eventually become resistant. Hence, it is essential to investigate the basis of anti-PD1/PDL1 resistance in order to devise tactics to surmount it.

Furthermore, intestinal microorganisms and their by-products can influence local and systemic anti-tumor immune reactions, thus enhancing immune responses and immunotherapeutic effects in cancer patients. The use of probiotics, prebiotic supplements, and FMT in animal experiments and clinical studies may be a viable way to enhance the effectiveness of tumor immunotherapy. It has been noted that the judicious choice of antibiotics and genetic engineering of bacteria may offer a theoretical foundation for intestinal flora and their metabolites to augment the immunotherapeutic properties of tumors. Due to the intricate nature of antitumor immunity and the distinctiveness of each person's gut microbiota, it is necessary to carefully choose patients and devise effective strategies. The gut microbiota can be modulated through a variety of methods, yet their effects remain a mystery, the sample size is limited, and there is a dearth of risk assessment data. Consequently, these techniques are not commonly employed and further investigation is necessary to guarantee their implementation. Recent advances in science and technology, such as next-generation sequencing, big data analytics, and artificial intelligence, will facilitate further exploration into the connection between the gut microbiota and immunotherapy. By pinpointing the particular gut microorganisms that have a positive effect on immunotherapy, as well as assessing the composition and proportions of the gut microbiota, it will be possible to evaluate the appropriateness of immunotherapy for each patient. A thorough examination of the role of gut microbiota in immunotherapeutic modulation necessitates the establishment of consensus-based guidelines for the clinical implementation of this promising adjuvant cancer therapy, which involves the use of precise and efficient techniques.

The focus of this review is on the growing body of research on the gut microbiota as a modifier of tumor immunotherapy efficacy. Despite this, this paper does not discuss other therapeutic strategies, such as radiotherapy for tumors or research on personalized

Table 1
Partially registered immunotherapy study to assess the therapeutic effects of gut microbiota.

Title	Identifier	Conditions	Interventions	Status	Locations
A Study of Diarrhea and Intestinal Flora Changes Caused by Pyrotinib in Breast Cancer	NCT05030519	Breast Cancer	Drug: Pyrotinib	Recruiting	China Zhejiang, Hangzhou, China
The Impact of Immunonutrition on Gut Microbiota-related Aspects in Colorectal Cancer and Gastric Cancer Patients	NCT04980950	Gastric Cancer Colorectal Cancer	Dietary Supplement: Impact Oral Nestlé Health Science, Cubitan® Nutricia, Nutridrink® Nutricia, Resource 2.0 Nestlé Health Science	Not yet recruiting	
The Gut Microbiome as an Indicator of Readiness for Head & Neck Cancer Surgery	NCT05061316	Cancer of Head and Neck Nutrition Aspect of Cancer	Dietary Supplement: Nestlé Impact Advanced Recovery	Recruiting	University of Alabama at Birmingham Birmingham, Alabama, United States
Gut Microbiome Dynamics in Metastasized or Irresectable Colorectal Cancer	NCT03941080	Colorectal Cancer Metastatic	Diagnostic Test: fecal sample Behavioral: questionnaire Diagnostic Test: Blood sample	Recruiting	Wilhelmina Ziekenhuis Assen, Netherlands Ziekenhuis Nij Smellinghe Drachten, Netherlands Treant Zorggroep Emmen, Netherlands (and 7 more …)
To Investigate the Role of Gut Microbiome in ADT Related Metabolic Changes in Prostate Cancer Patients	NCT04687709	Prostate Cancer		Recruiting	Prince of Wales Hospital Shatin, Hong Kong
Gut Microbiome in Colorectal Cancer	NCT04054908	Gastrointestinal Microbiome Neoplasm, Colorectal		Recruiting	University of California, San Francisco San Francisco, California, United States
Gut Microbiota and Cancer Immunotherapy Response	NCT04682327	Non-Small Cell Lung Cancer	Other: Response to anti-PD-1/PD-L1 Other: Non-response to anti-PD-1/PD-L1	Recruiting	Zhongshan Hospital, Fudan University Shanghai, Shanghai, China

clinical treatment of tumors.

Availability of data and materials

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Consent for publication

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CRediT authorship contribution statement

Yimin Zhou: Writing – original draft, Methodology. **Xiangdong Liu:** Supervision, Methodology. **Wei Gao:** Visualization, Investigation. **Xin Luo:** Visualization, Investigation. **Junying Lv:** Visualization, Investigation. **Yunshan Wang:** Writing – review & editing, Conceptualization. **Duanrui Liu:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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