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Gut microbiome and cancer immunotherapy

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ABSTRACT

Microbiome is becoming crucial in that the balance between human health and disease can be mediated by the gut microbiome. The gut microbiome can modulate the host immune system both locally and systemically. Cancer immunotherapy has emerged as a promising way in the treatment of patients with cancer. Accumulating evidence supports that microbiome affects the therapeutic efficacy of cancer immunotherapy, particularly immune checkpoint inhibitors. Here, we discuss the mutual relationship among gut microbiome, cancer, immunity, and cancer immunotherapy, with a focus on immunotherapy. Also, we briefly introduce the relevant challenges that affect the therapeutic efficacy and present the possible solutions.

1. Introduction

The human microbial ecosystem acts as an important role in human health and disease. The human microbiome is composed of a variety of microorganisms, such as bacteria, fungi, archaea, protozoa and virus, that reside on the surface of our body's epithelial barrier [1,2]. And the gut microbiome contains approximately 3×10^{13} bacteria, most of which are symbiotic with the host [3]. Multiple physiological functions can be affected by the microbiota, especially metabolism, inflammation and immunity [4,5]. When the intestinal micro-ecological system is changed, some commensal bacteria can rapidly proliferate and acquire pathogenic features known as pathobionts, including Clostridium difficile or vancomycin-resistant Enterococcus [6,7]. The gut microbiome interacts with epithelial cells and stromal cells to play various vital regulatory functions. For example, it can regulate barrier function, maintain mucosal immune homeostasis and host-microbial symbiosis, prevent pathogen infection, control overgrowth of pathological organisms, and regulate metabolism, including vitamin synthesis and metabolism of indigestible dietary fiber [8–12]. Therefore, a healthy body is inseparable from an integrated gut epithelium with specific function, and the gut microbiome, immune cells and mucosal barriers together maintain the intestinal epithelial homeostasis [13].

Cancer immunotherapy has become an emerging way in the treatment of patients with cancer. It utilizes the immune system to exert an anti-tumor effect. Immune checkpoint inhibitors (ICIs), as novel immunotherapeutic agents, have yielded promising clinical results in advanced hematologic malignancies, as evidenced by monoclonal antibodies (mAbs) blocking the cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) [14–17]. However, in some patients, primary or acquired resistance occurs during treatment, which hinders the widespread clinical application of ICIs [18]. Given this, choosing the optimal candidate patients is essential to avoid drug resistance and improve the efficacy of ICIs. In addition, major efforts to overcome resistance to immunotherapy are ongoing [19].

Accumulating evidence supports that the gut microbiome plays an important role in cancer treatment [20]. Intestinal microbial components have profound effects on the peripheral immune system, including in the context of cancer [21]. Recent studies have demonstrated that the gut microbiome affects the therapeutic efficacy of ICIs against cancer [22–26]. Of note, destruction of the gut microbiome, known as “intestinal dysbiosis”, has been epidemiologically related with various chronic inflammatory diseases [27]. Here, we discuss the relationship among the gut microbiome, cancer, immunity, and cancer immunotherapy, with a focus on immunotherapy. Also, we briefly introduce the relevant challenges that affect the therapeutic efficacy and present the possible solutions.

2. Microbiome and cancer

All host-related microorganisms are obtained by vertical transmission after birth and then continue to evolve via environmental exposure across the whole life. The gut microbiome plays a vital role in the innate and acquired immune responses. A delicate balance among

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inflammation, infection, and tolerance of food and symbiotic antigens can be achieved by the gut microbiome [27,28]. In addition to the effects on local immunophysiology, the gut microbiome plays a systemic role throughout the organism [28]. Compared to wild free-living animals, for instance, laboratory mice maintained under specific pathogen–free (SPF) conditions lack the key host fitness-promoting properties [29]. In view of this, prolonged immunomodulatory effects are produced by transferring the gut microbiome of wild-type mice to laboratory mice, and even after several generations of reproduction, the effects remain. Thus, it is advantageous for combating viral infection as well as mutagenic and inflammation-induced carcinogenesis [29].

It has been discovered that the microbiome is closely related to the occurrence and development of a variety of cancer types in the epithelial barrier and sterile tissues [30–33]. Symbiotic ecosystems that inhabit the gut or other mucosa perform a role in both local and distal carcinogenesis. On the one hand, microbiome can provide toxic metabolites or carcinogenic products directly as cancer-transforming agents [34]. On the other hand, it can indirectly play a role in promoting cancer by the induction of inflammation or immunosuppression [34]. Furthermore, through fecal microbial transplantation (FMT), the tumor-prone phenotypes could be transferred from gene-knockout mice without some immune-related genes (e.g., Tbx21, Nod2, Nlrp6 or Tlr5) to other normal mice [30]. In contrast, there is growing evidence that bacteria play an active role in fighting cancer distant from gut, by enhancing the host anti-tumor immunity [35–38]. Related studies have shown that a dose-dependent relationship occurs between antibiotic use and cancer risk [35]. Also, some anti-cancer treatments were observed that the therapeutic effects were reduced in germ-free (GF) mice and in mice without specific immune-potentiating bacterial species as well as in mice with broad-spectrum antibiotics [26,39–42]. The limited therapeutic efficacy is due to the absence or manipulation of the intestinal microbiota. The delicate mechanism, by which the microbiome can increase the anti-cancer immune response caused by treatment, may vary depending on the mode of treatment. Cyclophosphamide, for instance, resulted in the translocation of the small intestine–residing Enterococcus hirae to the spleen and the accumulation of Barnesiella intestinihominis in the colon, both of which contributed to playing a coordinated immune stimulation in the anti-tumor immunity [43]. It was attributed to the increased permeability of the upper gastrointestinal tract. To confirm these experimental results, some independent retrospective analyses in a cohort of patients with metastatic lung, kidney, and bladder cancer showed that antibiotics played a detrimental role in mAbs targeting PD1/PD-L1 [26]. Moreover, gut bacteria regulated the risk of infection and graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (ASCT) in hematological malignancies. Early application of systemic broad-spectrum antibiotics was correlated with increased GVHD and transplant-related mortality, possibly by the depletion of the protective Clostridiales and Blautia in the gut microbiota [44].

In summary, all of these studies provided a basis for identifying “good” microorganisms that may confer anti-cancer activity.

3. Gut structure, microbiome and immunity

Several trillions of microbes exist in human organism. During the development, microorganisms constantly interact with the host in many parts of the body such as the skin and mucosal surfaces (Fig. 1). Thus, it is conceivable that microorganisms exert a variety of extremely important roles in host function, including immunity [3,45].

The intestinal mucosa comprises a single epithelial cell layer that is composed of intestinal epithelial cells (IECs) and intraepithelial lymphocytes (Fig. 1). This unique structure promotes the interaction with the immune system. Paneth cells and goblet cells are localized in the IECs, secreting antimicrobial peptides and mucus respectively, which further cover the epithelium. The lamina propria is a connective tissue layer that is positioned beneath the mucosal layer, and contains Peyer's patches and various immune cells, such as antigen-presenting cells (APCs), innate lymphoid cells, T and B cells. This intestinal-associated lymphoid tissue is a typical representative of the largest component of the in vivo immune system and plays a critical role in local and systemic immune responses.

Local immunity is facilitated by pattern recognition receptor-mediated recognition of pathogen-associated molecular patterns (PAMPs). Pattern recognition receptors (PRRs) include Toll-like receptors (TLRs) on the IECs and innate immune effectors in the gut, while PAMPs contain lipopolysaccharide and flagellin. Also, local immune responses can be influenced by metabolites generated by bacteria, primarily via the production of short-chain fatty acids (SCFAs). In many pivotal activities, it has been proved that SCFAs could enhance immunity due to the production of IgA by plasma cells [46]. IgA works not only by blocking bacterial adhesion to epithelial cells, but also directly by affecting bacterial virulence [47,48].

The draining lymph nodes of the gut are located in the mesentery of the small intestine and colon, called the mesenteric lymph nodes (mLNs). Within the mLNs, the commensal bacteria transform the adaptive immune responses and then affect the differentiation of naive T cells. PAMPs are used to induce maturation of APCs, including dendritic cells (DCs). When the DCs mature, they enter into the mLNs, where they communicate with and further promote naive T cells to develop into $CD4^+$ T cells, particularly $CD4^+$ T regulatory cells (Tregs) and T helper 17 (Th17) cells, both of which have intestinal tendency [49,50]. Activated T cells act as a key role in intestinal homeostasis, as evidenced by Tregs-induced mucosal tolerance and production of immunosuppressive cytokines (e.g., IL-10). Of note, continuous crosstalk occurs between intestinal symbionts and mucosal T cells (e.g., Tregs) because bacterial metabolites such as SCFAs promote the maintenance of these cells at the intestinal level. The function of SCFAs relies on their capacity to suppress histone deacetylase activity, indicating the presence of epigenetic regulation [51]. Alternatively, the development of Tregs is mediated by a pathway that relies on polysaccharide A and TLR signaling to DCs [52,53]. Th17 cells, serving as a defined subset of $CD4^+$ cells, are promising in the lamina propria of the gut, and perform a critical role in preventing pathogen infection. Since cytokines secreted by Th17 cells, including IL-17, induce IECs to develop tight junctions and secrete anti-microbial proteins, Th17 cells also play a role in mucosal immunity [54]. IL-17 can further lead to the release of other inflammatory cytokines. Also, neutrophils can be recruited from the blood circulation to the intestinal microenvironment. In GF mice, Th17 cells were significantly deficient, but it could be induced by a specific bacterial subpopulation, called segmented filamentous bacteria [55,56].

In addition, systemic immune responses can be shaped by microbiome-mediated immune cell priming. When DCs present antigens from commensal bacteria in the mLNs of the intestine, B cells and T cells, including Tregs and Th17 cells, can travel throughout the body and promote immune responses against distant identical antigens, or against other antigens by cross-reacting with similar epitopes [57]. Strikingly, Th17 cells are functionally plastic in that they can alter their cytokine release on the basis of the local inflammatory or non-inflammatory conditions [58].

Microecological balance, termed eubiosis, is of importance in maintaining immunity. A rich and diverse microbiota can improve an infant's adaptive immune response to various vaccines [59]. By activating the TLR signaling pathway as a natural vaccine adjuvant, specific microbial components can also elicit an immune response [60]. On the contrary, ecological disorder, called dysbiosis, can lead to the destruction of the balance in the gut microbiome. It has the following characteristics: reduced diversity and relative instability of the microbiota, and potential accumulation of opportunistic pathogens [61]. Of course, dysbiosis can bring about a series of alterations [62]. For example, mucosal barrier is disrupted and local and systemic immune responses are impaired. Intestinal bacteria translocate to mLNs and

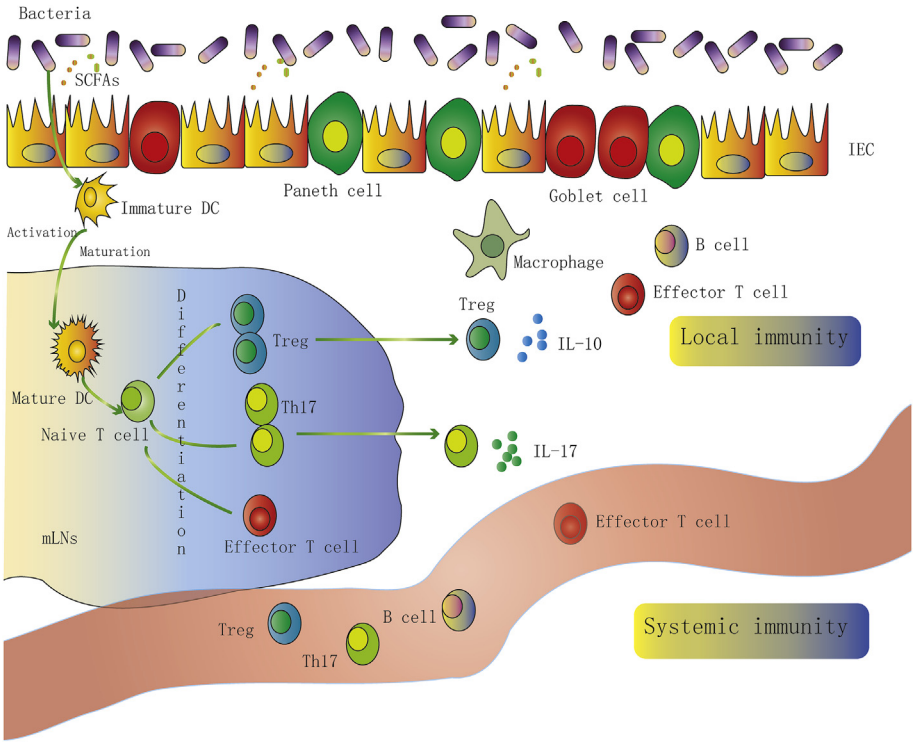

Fig. 1. The gut structure, microbiome and immunity.
The gut microbiome has a profound effect on the host immune system, both locally and systemically. Intestinal mucosa comprises a single epithelial cell layer that is composed of intestinal epithelial cells (IECs) and intraepithelial lymphocytes. Paneth cells and goblet cells are localized in the IECs, secreting antimicrobial peptides and mucus respectively. Bacterial metabolites (e.g., SCFAs) or bacteria themselves can activate local DCs to migrate to the mesenteric lymph nodes (mLNs). Mature DCs further activate naive T cells to differentiate into effector T cells, Tregs or Th17 cells, which can migrate back into the intestinal mucosa or into the systemic circulation. For local immune responses, Tregs secrete IL-10 and act to produce a local anti-inflammatory cytokine environment. Cytokine secretion from Th17 cells including IL-17 induces IECs to develop tight junctions and secrete antimicrobial proteins, and IL-17 can further lead to the release of other inflammatory cytokines. For systemic immune responses, it can be shaped by microbiome-mediated immune cell priming. When DCs present antigens from commensal bacteria in the mLNs of the intestine, B cells and T cells, including Tregs and Th17 cells, can enter the systemic circulation and promote immune responses against distant identical antigens, or against other antigens by cross-reacting with similar epitopes.

enter the peripheral circulation. The cytokine environment in the intestinal mucosa and mLNs changes and tends to an inflammatory phenotype. Th17 cells and effector T cells are activated. Eventually, a deep inflammatory state is caused locally and throughout the body [62].

In brief, gut microbiome profoundly influences the immune system both locally and systemically. Also, the immune system can alter the gut microbiome at different levels.

4. Microbiome and immunotherapy: response and toxicity

As mentioned above, gut microbiome plays an irreplaceable role in immunity. Similarly, the microbiome also acts an important role in cancer immunotherapy, particularly ICIs. Initially in the mouse models, the gut microbiome was found to modulate the response to immune checkpoint blockade [41,42]. Nowadays, there is growing evidence that the gut microbiome may play a key role in regulating the response of immunotherapy. Many of these findings have been verified in patients receiving immunotherapy such as ICIs [22–26].

Firstly, the response to an immune checkpoint inhibitor, anti-PD-1/PD-L1 or anti-CTLA-4, may be affected by the components of the gut microbiota [41,42]. Regarding PD-1/PD-L1 blockade, mice with different microbes had significant differences in response to treatment [42]. Analysis of the gut microbiome showed that Bifidobacterium species were increased significantly in mice with slow tumor growth and beneficial responses to anti-PD-1 therapy. The better effect from mice with a more favorable microbiota can be transferred to other mice by FMT or co-housing. In addition, mice with unfavorable gut microbiota were provided with oral probiotics containing Bifidobacterium, which in turn increased the anti-tumor efficacy of PD-L1 blockade. This effect mainly arose from the enhancement of DC maturation, thereby improving the tumor-specific $CD8^+$ T cell activity [42]. After anti-CTLA-4 treatment, the abundance of gut microbiota obviously varied in mice, as evidenced by the relative increase of Bacteroidales and Burkholderiales and the decrease of Clostridiales [41]. Oral feeding of Bacteroides fragilis with Bacteroides thetaiotaomicron or Burkholderia cepacian enhanced the efficacy of anti-CTLA-4 therapy by triggering a Th1 response and promoting DC maturation. However, in GF mice and SPF mice using broad-spectrum antibiotics, the action of anti-CTLA-4 therapy was remarkably decreased. The effect could be reversed through FMT from patients with dominant Bacteroides species [41].

In addition, the gut microbiota exerts a vital role in patients with immune checkpoint blockade, representing a fundamental to clinical transformation. Recent studies have confirmed the importance of gut microbiota [22–26]. With anti-PD-1/PD-L1 treatment, overall survival and progression-free survival rates were significantly higher in epithelial tumor patients who did not receive antibiotics for routine indications compared with tumor patients receiving antibiotics [26]. This phenomenon indicates that the use of antibiotics may destroy the gut microbiota, thereby impairing the anti-tumor immunity and the response to immune checkpoint blockade [26]. Whole metagenomic sequencing in stool samples from these patients showed that patients responding to PD-1 blockade had different gut bacterial compositions, which were abundant in Akkermansia and Alistipes [26]. Prior to anti-PD-1 treatment, FMT was implemented in GF mice with fecal samples from responding patients (R) and immunity was enhanced, whereas immunity of GF mice receiving FMT of non-responders (NR) could be recovered using Akkermansia muciniphila alone or combined with E. hirae [26]. Interestingly, A. muciniphilia was correlated with increased immune cell infiltration in tumor, as $CCR9^+CXCR3^+CD4^+$ T cells were recruited to the tumor bed and the ratio of $CD4^+$ T cells to $CD4^+FoxP3^+$ T cells (Tregs) was increased [26]. In patients with metastatic melanoma, the efficacy of anti-PD-1 therapy was also influenced by gut microbiota [24,25]. The diversity of gut microbiota was significantly increased in patients responding to PD-1 therapy, and certain microorganisms were relatively more abundant, such as Clostridiales, Ruminococcaceae and Faecalibacterium [25]. However, for non-responding patients, they had lower diversity of intestinal bacteria and higher Bacteroidales abundance [25]. Analysis of both the compositions of the gut microbiota and the immunological profiling in the tumor microenvironment demonstrated that the expression of cytotoxic T cell markers and antigen processing and presentation were augmented in patients with favorable gut microbiota compared to patients with unfavorable gut microbiota [25]. Another study also showed that difference in gut microbiota occurs on response to ICIs [24]. In

particular, patients who responded to PD-1 blockade were rich in Bifidobacterium longum, Collinsella aerofaciens and Enterococcus faecium. Transferring responder stool samples to GF mice also successfully reproduces the dominant phenotype: slower tumor growth and improved therapeutic effects compared to mice receiving non-responder stool. The above results were obtained by an increase in $CD8^+$ T cells and a decrease in Tregs in the tumor microenvironment [24].

Analysis of differences in response to immune checkpoint inhibitors may be closely associated with several different factors, such as differences in the techniques and the reference databases applied to analyze the samples. Other factors, including geography, diet and lifestyle, may also be the cause of some differences observed.

However, the gut microbiota can also cause toxicity to the immune checkpoint blockade. The effects of gut microbiota on toxicity were investigated in animal models and human cohorts [22,23,41,63]. Melanoma patients with anti-CTLA-4 treatment, who were rich in Bacteroidetes and various genetic pathways referring to polyamine transport and B vitamin synthesis, did not develop colitis [63]. This kind of toxicity may be associated with the known effects of these bacteria involving in Tregs differentiation [53,64]. Other studies have also shown that a higher risk of colitis was present in patients with higher Faecalibacterium prausnitzii abundance and lower Bacteroides abundance after anti-CTLA-4 therapy [22,23]. Bacteria related with response and toxicity have distinct taxa, some of which have overlapping features. According to related studies, the bacterial taxa involved in both response and toxicity were within the Ruminococcaceae family of the Firmicutes phylum upon the ICIs [22,23,25]. In contrast, the bacterial taxa lacking response to ICIs were within the Bacteroidales order of the Bacteroidetes phylum, but a higher abundance in these taxa usually reduces the incidence of toxicity [22,23,25,63].

Overall, the influence of the gut microbiome on the therapeutic efficacy is undeniable. The gut microbiome can both modulate the anti-tumor immune responses and regulate the responses to immune checkpoint inhibitors.

5. Challenges and possible strategies to improve gut microbiome in cancer treatment

Despite the promise of the gut microbiome in cancer therapy, particularly immunotherapy, there are still some challenges that need to be addressed (Fig. 2).

First of all, the existence of unfavorable bacteria in the gut can negatively affect the efficacy of immunotherapy. Currently, antibiotics can be used to remove harmful bacteria, but may also pose certain risks including dysbiosis due to lack of specificity. Prebiotics, including dietary or chemical entities, should facilitate the colonization and relative expansion of particular bacteria, which may have a beneficial effect on anti-tumor immunity. In this respect, the components of dietary fiber can be metabolized to produce short-chain fatty acids with immunomodulatory properties, and related studies have confirmed this [65]. However, the role of prebiotics depends on the particular bacteria already present in the host. Thus, the combination of prebiotics and specific bacteria, called synbiotics, may be promising. Of note, in the food industry, bacteriophages have been applied to eliminate unfavorable bacteria due to their high selectivity for specific bacterial species [66].

In addition, despite the encouraging results of FMT in the treatment of refractory Clostridium difficile diarrhea [67], FMT requires consideration of several key factors, especially the choice of an optimal donor. Ideally, the FMT donor should be an individual with a wide variety of microbial compositions, including favorable bacteria. Up to now, Bifidobacteria spp. [24,42], Akkermansia muciniphilia [26], E. hirae [43], and Bacteroides spp [41]. have been regarded as favorable bacteria, which can effectively improve anti-tumor immunity and better control tumor growth in vivo. It is worth noting that the transfer of pathogens is also a potential problem, requiring careful screening regardless of bacteria, viruses or parasites. Some bacteria seem to play a role in the inflammation-induced carcinogenesis. Transferring the gut microbiome of patients with colorectal cancer to GF mice can cause dysplasia, polyp formation and tumorigenesis, which can't occur during normal donor transplantation [68]. Moreover, an ideal alternative to transferring commensal bacteria from a particular donor is to utilize the specific bacteria, either alone or in combination. The strategy will involve three aspects, firstly accurate bacterial isolates that support the improvement of anti-tumor immunity in the host, followed by culture conditions that support their in vitro expansion, and finally encapsulation protocols that maintain biological activity. Available sequencing methods may prioritize the detection of the most abundant bacteria with favorable clinical results, while ignoring lower abundant bacteria. However, these bacteria may be functionally important as well. Thus, careful separation, culture and mechanistic testing of rare microorganism species are worth considering.

Moreover, the species of bacteria identified by different research teams could be inconsistent in the treatment of cancer [22,41]. The study by N. Chaput et al. discovered that B. fragilis was in low proportion at baseline and higher Bacteroidales ratio hindered the anti-tumor effect of anti-CTLA-4 in metastatic melanoma patients [22]. However, Marie Vétizou et al. found higher B. fragilis ratio contributed to tumor regression [41]. Furthermore, the research team of N. Chaput et al. observed that several Firmicutes, such as Faecalibacterium genus, butyrate producing bacterium and G. formicilis, were associated with higher response rate as well as longer progression-free survival (PFS) and overall survival (OS) [22]. Also, this team noticed that the use of antibiotics did not affect the composition of the main microbiota and bacterial species that may affect the efficacy [22]. This phenomenon is inconsistent with previous studies as the use of antibiotics impaired the efficacy of ICIs, deserving further investigation [25,26,69]. Several aspects could account for the discrepancies between different trials. First of all, the preference occurs in the FMT and differences exist between mouse and human models, both of which restrict the extrapolation of conclusions [22]. For example, tumor established in mice through transplanting tumor cells may not accurately represent human response to treatment [70,71]. On the one hand, compared with the actual tumor microenvironment, the xenograft model lacks the process of multi-step carcinogenesis and chronic inflammation. On the other hand, injection of tumor cells into mice is usually accompanied by tumor cell death, resulting in the initial vaccination effect [71]. Second, in mouse experiments, it is difficult to rule out interference results from other bacterial species due to limitations in qPCR analysis for certain species of Bacteroidales [22]. It is noteworthy that, except for patients with treatment-induced colitis, anti-CTLA-4 did not cause significant changes in intestinal microbial composition [22], contrary to the conclusions reached by Marie Vétizou et al. [41]. Interestingly, a recent study by Mao K et al. noted that innate and adaptive immune responses affected the state of the gut microbiota [72]. Accordingly, it is conceivable that the released T cells would reshape the gut microbiota, as evidenced by the altered number and proportion of certain bacteria, and even the changes in the morphology and function of the bacteria. Thus, a large number of studies should be conducted in the future to assess the impact of ICIs on the gut microbiota.

Additionally, it should be emphasized that there are differences between different studies. Such differences may include three aspects: patients with different genetic and nutritional patterns, clinical trials conducted in distinct geographic locations in the Europe or United States, and tumor types, such as melanoma, lung cancer and renal cell carcinoma. In view of these aspects, it has been found that bacteria normally related with health (e.g., Ruminococcacae, Akkermansiamuciniphila, and Bifidobacteria) or immunogenicity (e.g., Enterococci, Collinsella, and Alistipes) may be rich in responding patients with cancer [22,24,26,39,41]. A study in 541 patients with hematological malignancies showed that the gut microbiome at the time of diagnosis affected the likelihood of recurrence within 2 years after

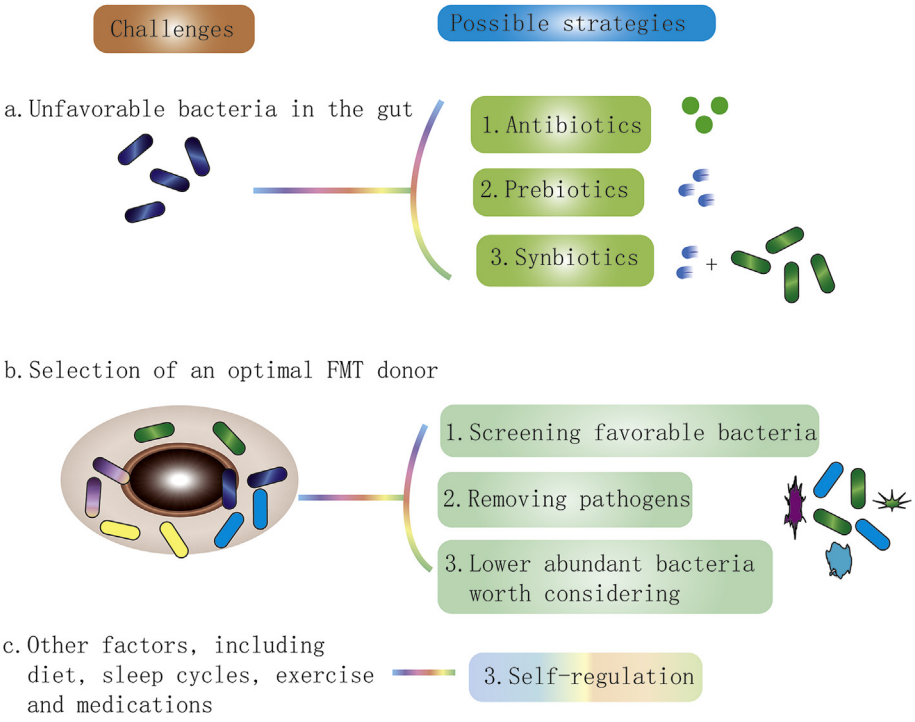

Fig. 2. Challenges and possible strategies to improve gut microbiome in cancer treatment.
a. Unfavorable bacteria in the gut can negatively affect the efficacy of immunotherapy. To solve this problem, antibiotics can be utilized to remove harmful bacteria, but may pose risks such as dysbiosis due to lack of specificity. Prebiotics, including dietary or chemical entities, can promote the colonization and relative expansion of particular bacteria, which may have a beneficial effect on antitumor immunity. Also, the combination of prebiotics and specific bacteria, called synbiotics, may be promising. **b.** Selection of an optimal FMT donor is critical for improving anti-tumor immunity. To date, some bacteria, including Bifidobacteria spp., Akkermansia muciniphilia, E. hirae and Bacteroides spp., have been regarded as favorable bacteria, which can effectively improve anti-tumor immunity and better control tumor growth in vivo. However, the transfer of pathogens is a potential pitfall that requires the removal of pathogenic bacteria. Moreover, current sequencing methods may prioritize the detection of the most abundant bacteria with favorable clinical results, while ignoring lower abundant bacteria. Thus, careful separation, culture and mechanistic testing of rare microorganism species are worth considering. **c.** Other factors, including diet, sleep cycles, exercise and medications, can regulate gut microbial composition and we can adjust these factors ourselves to enhance anti-tumor immunity.

allogeneic hematopoietic stem cell transplantation (ASCT). Of note, a highly abundant bacterial population mainly made up of Eubacterium limosum had a positive effect on prognosis [73].

Other factors, including diet, sleep cycles, exercise and medications, can regulate gut microbial compositions [74]. Therefore, these parameters may be relevant to the efficacy of immune checkpoint inhibitors and other immunotherapies.

6. Conclusions

The era of microbiomes has quietly come, and pioneering reports of preclinical and clinical research on the role of microbiome in cancer have made gut microbiome a promising strategy for cancer treatment. We have gained some insights into the effects of the microbiome on cancer and immunity, however, the underlying mechanisms are still less understood. Furthermore, some challenges remain to be solved regarding how to regulate the gut microbiome to improve the efficacy of cancer immunotherapy. It is unclear that which specific composition of the gut microbiome is most conducive to promoting an anti-tumor immune response, and there are a variety of treatments that alter the microbiome, which requires careful testing in the setting of clinical trials. Only by fully understanding these interactions can we learn to optimally regulate the gut microbiome to enhance host anti-tumor immunity and potentially improve immune surveillance.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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