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MINI-REVIEW

Role of gut microbiome on immunotherapy efficacy in melanoma

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ABSTRACT

The gut microbiota is considered a key component in many aspects of cancer pathophysiology and response to therapy. In particular, in recent years intriguing evidences has been emerging regarding the role of the intestinal microbiota in the response to immunotherapy and in promoting the development of adverse events, such as colitis. For this reason, studies are being carried out both on pre-clinical models and on humans to study how to predict the response to immunotherapy through the study of the microbiota or how to improve its clinical response through modulation. Promising data have recently been reported through modulation by probiotics or prebiotics, and in particular by fecal microbiota transplantation. The aim of this review is to analyze the evidence regarding the role of the microbiota in immunotherapy with a particular focus on melanoma.

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Introduction: gut microbiota and immune system

Gut microbiota influences several aspects of host immunity, in particular the relationship between microbiota and the immune system of intestinal mucosa is considered a key component in the maintenance of mucosal homeostasis.[1,2] This complex interaction is based on a coordinated set of innate and adaptive responses against pathogens, specialized populations of cells integrate local signals such as metabolites, cytokines and hormones that allow the induction of responses to preserve function and physiology of each tissue.[3] Gut microbiota modulates several aspects of the host immune system, for example *Bacteroides fragilis* is involved in the differentiation from naïve CD4+ to regulatory T cells (Treg cells), that are able to secrete anti-inflammatory cytokines in abundance as IL-10.[4]

In recent years, the interest in the interaction between microbiota and immune system is becoming increasingly important, particularly because immune modulation is taking hold in cancer treatment. In particular, it was recently introduced in clinical practice the immunotherapy that is able to target T-cell pathway to improve anticancer immune response.[5] To date, the most important approach in immunotherapy of cancer is based on the regulation of T cells by checkpoints inhibitors. In particular, the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 (PD-1) immune checkpoints are negative regulators of T-cell immune function, inhibition of these targets leads to increased activation of the immune system favoring cancer control.[6]

The relationship between gut microbiota and immunotherapy

The development of cancer immunotherapy over the past decade has revolutionized the therapeutic approach to multiple types of cancer for both solid and hematologic malignancies, including the management of a wide range of cancers associated with poor prognosis.[7]

Immunotherapy exploits several pathways to regulate the immune response in cancer treatment; however, the main evidence is in favor of the immune checkpoint inhibitors (ICIs) that aim to suppress the interaction between T-lymphocytes and their ligands by stimulating the T-cell mediated immune response against tumor-associated antigens.[8,9] ICIs exploit several mechanisms of action, for example were available monoclonal antibodies (mAbs) that interfere with programmed cell death protein 1 (PD-1) and its ligand (PD-L1).[10] Furthermore, mAbl targeting the cytotoxic T-cell antigen 4 protein (CTLA-4) can allow cytotoxic lymphocytes to snap off cancer cells.[11] Several evidences suggest that CTLA-4 blockade results in direct activation effector cells (CD4 + and CD8+), and anti-CTLA-4 monoclonal antibody therapy has considered a promising tool in a several type of cancers, particularly melanoma.[12]

In this scenario, gut microbiota was proposed as modifiers of clinical response to anticancer treatment. For instance, in a mouse model was reported that gut microbiota was involved in favoring the anticancer immune response, in particular was observed that gut microbiota was modified by cyclophosphamide altering the composition of microbiota in the gut promoting the translocation of bacteria into secondary lymphoid organs, suggesting a microbial driving mechanism to improve the anticancer immune response.[13] Later, the role of microbiota in ICIs treatment was reported by other preclinical studies that investigated the effect of gut microbiota on ICIs therapy efficacy. In particular, *Vetizou* et al.[14] confirmed that gut microbiota is involved in shaping the immune response to anti-CTLA-4 therapy against cancer cells. They reported that

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antibiotic-treated and germ-free mice were resistant to selected treatment whereas specific pathogen-free mice responded to anti-CTLA-4 treatment. Interestingly, after recolonization of intestinal mucosa with specific *Bacteroides* (*B. fragilis* and *B. thetaiotaomicron*) and *Burkholderiales cepacia* the CTLA-4 blockade was restored in non-responding mice. A further study confirmed the role of specific commensals in clinical response and the development of drug induced toxicity. Indeed, if baseline gut microbiota was enriched with *Faecalibacterium* spp. and *Firmicutes* spp, the clinical outcome of melanoma patients treated with ipilimumab was correlated with clinical improvement; however, ipilimumab-induced colitis was reported more frequently in the patients with enriched microbiota.[15] Moreover, similar results were reported in another study that confirmed the improved clinical response in patients with metastatic melanoma treated with anti-CTLA-4 therapy if gut microbiota was enriched by *Faecalibacterium* spp.[16]

Furthermore, several research lines addressed attention toward the role of microbiota in enhancing the efficacy of immunotherapy. Indeed, several studies suggest that also anti-PD-1 therapy efficacy is altered by gut microbiota composition, more specifically several microbiota signatures were indicated as potential biomarkers of immunotherapy efficacy in melanoma. For example, the administration of a mixture of *Bifidobacterium* spp, which included *B. breve* and *B. longum*, was correlated to the improving of tumor control by anti-PD-L1 characterized by altered immune response as demonstrated by the increased number of $CD8^+$ T cells in a mouse model of melanoma.[17]

Moreover, several evidences were reported about the microbiome alterations observed during immunotherapy. Specifically, a pioneering study reported several microbial signatures in melanoma patients treated with ICIs. For instance, *Bacteroides caccae* was more abundant in all patients treated with several immunotherapies, furthermore feces of patients receiving treatment with ipilimumab and nivolumab were enriched in *Faecalibacterium prausnitzii, Bacteroides thetaiotaomicron* and *Holdemania filiformis*, besides stools of patients receiving Pembrolizumab had higher levels of *Dorea formicogenerans*.[18]

More interesting data derived from a study by *Matson* et al. suggesting a role for gut microbiota composition in predicting clinical response to anti-PD-1 or anti-CTLA-4 regimens in patients with melanoma. In particular, the study reported higher abundance of *Bifidobacterium longum and adolescentis, Collinesella aerofaciens*, and *Parabacteiodes merdae* in the feces of responders patients, while non-responders patients were characterized by a microbiome more enriched in *Ruminococcus obeum* and *Roseburia intestinalis*.[19] Finally, further data suggesting the fundamental role of microbiome in modifying the response to immunotherapy were reported by *Gopalakrishnan* et al. who examined differences in gut microbiota between responders and non-responders melanoma patients treated with anti-PD-1 therapy. In this report *Faecalibacterium*, the *Ruminococcae* and the *Clostridiales* were overrepresented in responder patients, while non-responders patients showed a higher presence of *Bacteriodales*; interestingly the microbial signature was correlated with altered immune response that was characterized by more circulating CD4+ and CD8 + T cells with preserved cytokine responses in responders and by higher frequency of circulating regulatory T cells in non-responders.[20]

Improving immunotherapy efficacy by the modulation of gut microbiota

Intestinal microbiota substantially influences the efficacy of cancer immunotherapy.[21] Thus, the modulation of gut microbiota was proposed as new tool to improve cancer immunotherapy efficacy and was suggested to decrease related adverse effects.[22,23] Several preclinical and observational studies supporting the role of gut microbiota in improving the outcomes of cancer therapeutic, furthermore there are now several interventional studies examining the feasibility of microbiota modulation to improve therapeutic efficacy and reduce drug induced toxicity. Particularly, the microbiota can be modulated with several approaches, most notably in recent years they have been successfully used antibiotics, pro-prebiotics or fecal microbiota transplantation.[24,25] Several approaches will be discussed in the following section taking into account the current evidence available from mouse models and from clinical human studies. Unfortunately, the results relating to patients with melanoma are still limited; therefore, we will discuss also data relating to other cancers treated with immunotherapy assuming a similarity pending future confirmation from clinical studies.

Antibiotics (ATBs)

Several studies show that antibiotic treatment was detrimental to anti-CTLA-4 and anti-PD-1 therapies; those studies have proven that the use of antibiotics before and during ICI therapy is associated with worse outcome, both in animal models and, more importantly, in cancer patients. For instance, *Derosa* et al.[26] investigated patients with advanced renal cell carcinoma or non-small-cell lung carcinoma treated with anti-PD-1 who had taken antibiotics up to 3 months prior to receiving ICIs therapy, interestingly these patients had a worse clinical outcome, suggesting that antibiotics were associated with reduced clinical response. Furthermore, another study confirmed a negative effect of ATB-related dysbiosis in clinical efficacy of ICIs, in particular, broad-spectrum antibiotics, defined as active against gram-negative, gram-positive, and anaerobic bacteria, were associated with the greatest relative risk of ICIs non-response.[27] These data are of particular relevance in consideration of the recurrent multidrug-resistant infections in patients with cancer and the prognostic implications during immunotherapy.[28]

Probiotics

Probiotics are defined as "live microorganisms, which if taken in adequate quantities, confer a health benefit to the host", according to FAO/WHO definition.[29] The ingestion of beneficial bacterial strains can improve microbial dysbiosis, exclude pathogenic bacteria, and modulate the immune status, introducing exogenous bacteria and establishing either transient or stable colonization.[30] Studies have suggested beneficial effects

of probiotics on reducing the development of several types of cancers and mucosal inflammation in animal models, however, supporting clinical data in humans are limited.[31] For example, *Hibberd* et al.[32] investigated the role of microbiota composition of patients with colon cancer and the potential to modify the colonic microbiota with probiotics. More specifically, several differences were reported between fecal microbiota of cancer patients compared to control, as increased microbial diversity and enrichment of *Fusobacterium, Selenomonas* and *Peptostreptococcus* in cancer patients; however, patients who received probiotics had an increased abundance of beneficial butyrate-producing bacteria, as *Faecalibacterium* and *Clostridiales spp*., suggesting a potential tool in cancer treatment based on the ability of orally administered probiotics to alter the tumor microenvironment.

These pioneering experiences have allowed researchers to hypothesize new frontiers in the use of probiotics, and in particular probiotics was proposed as enhancers of the response to immunotherapy; therefore, several clinical studies are ongoing (clinicaltrial.gov). In particular, an ongoing trial (NCT03817125) in metastatic melanoma patients undergoing immunotherapy (anti-PD-1) employing a defined orally administered microbial for modulation (SER-401) is intended to assess safety, clinical response, as well as change in gut microbiota and immunity. Another ongoing clinical trial of a proprietary bacterial strain (MRx0518) in combination with anti-PD-1 therapy is enrolling patients with melanoma, bladder cancer, non-small cell lung cancer, and renal cell carcinoma (NCT03637803).

Prebiotics

Prebiotics were defined as a substrate that if selectively used by host microorganisms is able to confer a health benefit.[33] The use of prebiotics, known as dietary elements indigestible or absorbable by human GI tract and specifically used by gut microbes, should increase the colonization of bacteria and increased production of their beneficial metabolites, which may have a positive effect on anti-tumor therapy.[31] Indeed, a new study published in 2020 showed that mucin and inulin might help boost the immune response against melanoma.[34] In particular, the researchers studied in a mouse model how prebiotics can enrich bacterial taxa that promote anti-tumor immunity to treat melanoma. More specifically, data demonstrated the role of insulin in the control of tumor growth and in enhancing the efficacy of an immunotherapy against melanoma while delaying the emergence of drug resistance; besides, in germ-free mice mucin is not able to inhibit tumor growth, suggesting that the gut microbiota is required for the development immune response supporting anti-cancer treatment. The data from this study should be confirmed by clinical studies on patients, but represent a starting point for the development of future clinical trials.

Synbiotics

The mixture of prebiotics and probiotics is defined as synbiotics. The mechanism of action of synbiotics is based on the synergic action of the two components, indeed prebiotics elements selectively stimulate growth or metabolism of probiotic bacteria, promoting the colonization of the gut by probiotics;[35] in addition they can also stimulate the growth of some commensal bacteria.[36] Synbiotics may provide additional benefits also in cancer patients in consideration of the potential synergistic effects of the two components in the beneficial modulation of gut microbiota.[37] For example, a mixture containing *Lactobacillus reuteri* and inulin-type fructans is able to improve the expression of antimicrobial proteins controlling intestinal barrier function and gut immunity in leukemic mice; in particular, these molecular pathways are favored by the restoration of *Lactobacillus* and reduction of *Enterobacteriaceae*. Furthermore, synbiotics favored a prolonged survival and reduced cancer proliferation,[38] suggesting a potential role as adjuvant of anti-cancer treatment.

Postbiotics

Postbiotics have distinct characteristics and advantages over prebiotics and probiotics, and this definition is emerged to denote that microbial fractions might offer physiological benefits to the host by providing additional bioactivity modulating the microbiota.[39] In particular, postbiotics are not depending by the cultivation of specific bacteria and do not suffer from complex microbial community dynamics. In consideration of their unique characteristics, postbiotics are considered as a novel approach for adjuvant therapy in patients with cancer.[40] Unfortunately, to our knowledge, there are limited evidences in literature about the use of postbiotics in the improvement of cancer treatment efficacy.

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) was defined as the infusion in the gastrointestinal tract of manipulated feces from a donor to a recipient affected by disorder related to intestinal dysbiosis with the purpose of reconstitute a healthy gut microbiota.[41] To date, FMT is indicated in the treatment of recurrent *Clostridiodes difficile* infection with excellent results and was proposed for the treatment of other chronic gut-related disorders.[42,43] In consideration of issues discussed above that underlined the role of the microbiome in modulating the response to immune modulation in cancer treatments, FMT was proposed as adjuvant treatment of immunotherapy.[44] Furthermore, several evidences were recently reported about the use of FMT to improve the efficacy of immunotherapy or to reduce side effects. Recently, *Wang* et al.[45] reported data on ICI-associated colitis successfully treated FMT; they also reported the restoration of an eubiotic intestinal microbiota that promote the relative increase of Tregs within the colonic mucosa. These findings were confirmed by a further study involving patients with metastatic renal cell carcinoma which have developed diarrhea induced by tyrosine kinase inhibitors (TKI), FMT was successfully used to treat patients, results demonstrated the resolution of diarrhea 4 weeks after the procedure.[46]

Encouraging results are also published about the use of FMT in favoring the response to immunotherapy,

although the data are still limited to animal models. For example, *Gopalakrishnan et al.*,[20] transferred the fecal material from responder or non-responder patients to anti-PD-1 therapy into melanoma-bearing germ-free mice demonstrating that 4 weeks after treatment mice treated with fecal material derived from responders had a significant reduction of the tumor volume compared to control group. Similarly, *Matson et al.*[19] transferred fecal material from human responders or non-responders into GF mice, followed by the implantation of melanoma cells. Interestingly, results reported that mouse treated with fecal material from non-responding patients to anti-PD -1 showed faster cancer growth rate, while slower growth rates were observed for mice reconstituted with fecal material from responding patients. Further data confirming the fundamental role of modified microbiota derived from a study in which were transferred feces from cancer patients who responded to ICIs into mice treated with antibiotics observing amelioration in antitumor effects of PD-1 blockade, whereas FMT from non-responding patients failed.[47]

Based on these promising results, several clinical trials approaching FMT in order to improve cancer therapy are still ongoing (clinicaltrial.gov) (Table 1). A clinical trial (NCT038 19296) is currently assessing the role of the gut microbiome and effectiveness of a fecal transplant on medication-induced gastrointestinal complications in patients with melanoma or genitourinary cancer in patients treated with immune-checkpoint inhibitor drugs. Another clinical trial involves melanoma patients with PD-1 (Pembrolizumab) resistant or refractory melanoma (NCT03341143). This study aims to determine if FMT improves effects of ICIs. A further trial evaluates the safety and efficacy of FMT in combination with Nivolumab in subjects with metastatic or inoperable melanoma or NSCLC (NCT04521075). A similar study, (NCT03772899), examines the safety of combining FMT and pembrolizumab or nivolumab in melanoma patients.

Although the clinical relevance of FMT in association with ICIs seems promising and is increasing worldwide, it is necessary to be cautious regarding these trials and looking for standardized research approaches.

Final remarks and future perspectives

In this review, we analyzed the evidence on the role of the gut microbiota in immunotherapy with a particular focus on melanoma. Especially from the animal model, interesting evidences have emerged regarding the fundamental role of the microbiome in the development and progression of cancer, and particularly promising evidence has emerged in favor of the modulation that is able to enhance the response to immunotherapy. Furthermore, an aspect that should not be underestimated is the appearance of adverse effects induced by immunotherapy, such as colitis, which would seem to be directly related to particular microbiological signatures. It is therefore understood how the modulation of the intestinal microbiota represents a promising and interesting tool in the treatment of cancer. Various tools have been used with encouraging results, from traditional probiotics and prebiotics to the innovative and intriguing fecal microbiota transplantation. On the basis of these observations there is a growing enthusiasm toward modulation of the microbiota in cancer and in particular in immunotherapy. However, it should be noted that the available studies are still preliminary and have many limitations. In fact, there is a lot of sample variability, both in terms of the type of patient enrolled, both in terms of the immunotherapy administered and especially in relation to the modulation methodology of the microbiota used. Furthermore, the risk of transmission of bacteria or pathogens in often defied and immunosuppressed patients should not be underestimated, in particular with regard to fecal microbiota transplantation, indeed to date strict screening protocols are followed in the selection of the donor, but transmission of unknown pathogens cannot be excluded. For this series of observations, it can be concluded that further preclinical and clinical studies are needed to implement and standardize gut microbiota modulation in immunotherapy. In particular, it is necessary to identify with greater precision the microbial signatures that predispose to the development of adverse effects or a lower response to immunotherapy; moreover,

Table 1. Clinical Trials from the database "clinicaltrials.gov" involving FMT in the treatment of melanoma, updated to 8 march 2021.

Title of the study	Clinical trial number	Phase	subjects involved	ICIs	Primary outcome
Altering the Gut Microbiota of Melanoma Patients who failed immunotherapy using Fecal Microbiota Transplantation (FMT) from responding patients	NCT03353402	1	40 MM	PD-1 inhibitor	Incidence of FMT-related Adverse Events
Phase II Feasibility Study of Fecal Microbiota transplant (FMT) in Advanced transplant in melanoma Patients not responding to PD-1 Blockade	NCT03341143	2	20 MM	PD-1 inhibitor (nivolumab or pembrolizumab	Objective Response Rate
Inducing remission in Melanoma Patients with Checkpoint inhibitor therapy using Fecal Microbiota Transplantation	NCT04577729	Not Applicable	60 MM	Not specified	Progression free survival
A Phase Ib, Single Center Trial to Evaluate the Safety and Efficacy of Fecal Microbial Transplantation in Combination With Nivolumab in Subjects With Metastatic Melanoma or Non-small cell lung Cancer	NCT04521075	1b	50 MM and NSCLC	Nivolumab	Incidence of FMT-related Adverse Events
Role of Gut Microbiome and Fecal Transplant on Medication-Induced GI Complications in Patients With Melanoma or Genitourinary Cancer	NCT03819296	1	800 melanoma or genitourinary cancer	Not specified	Incidence of adverse events

MM (metastatic melanoma), NSCLC (Non-Small Cell Lung Cancer).

it will be necessary to identify specific probiotic, prebiotic mixtures, and human fecal biomass that can selectively be used to improve the clinical response. Finally, the modulation of the microbiota appears as an intriguing therapeutic tool in the treatment of cancer, further studies are needed but the greater dissemination of knowledge on the complex interaction between the microbiota and the immune system allows us to have many hopes in the near future.

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No potential conflicts of interest were disclosed.

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