Intestinal Microbiota in Cancer Immunotherapy

Subjects: Immunology

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Despite the great achievements of cancer immunotherapy in a variety of tumors, tumor heterogeneity and drug resistance still plague patients and clinical researchers. In particular, the occurrence of immune-related adverse events forces patients to discontinue cancer immunotherapy. Therefore, it is urgent to optimize cancer immunotherapy and improve the efficacy of immunotherapy. With the iteration of sequencing technology, the microbiome, as the second set of genomes in the body, has been proven to be involved in immunity and metabolism. More and more studies are gradually shifting the perspective to the intestinal microbiota and cancer immunotherapy. The intestinal microbiota reactivates and modulates immune cells in immunotherapy and is expected to become a biomarker for predicting immune efficacy. Targeting to improve the intestinal microbiota can enhance anti-tumor immunity. This advantage is beneficial to control related adverse symptoms and expand the beneficiary population of cancer immunotherapy. This finding can help clinicians comprehensively evaluate the effect of tumor screening and tumor treatment. Therefore, the innovative combination of gut microbiota and cancer immunotherapy is expected to be an active strategy to enhance individualized immune responses.

microbiota   immunotherapy   metabolism

1. Introduction

Currently, immunotherapy is considered one of the most cutting-edge technological revolutions in the field of clinical oncology. Immune checkpoint inhibitors (ICIs) (such as anti-programmed death receptor 1/programmed death ligand 1 (PD-1/PD-L1), anti-cytotoxic T lymphocyte antigen 4 (CTLA-4)) indirectly exert active and effective anti-tumor immunity by inducing suppressed T cell activation [1]. Based on a large amount of clinical and medical evidence, some ICIs have been approved by the drug regulatory agency for trials or treatments of various malignant tumors [2]. However, most patients still cannot fully benefit from ICIs, which are often accompanied by primary drug resistance or immune-related adverse events [3].

In order to improve the titer of immunotherapy, actively seeking to serve biomarkers for ICIs response and toxicity prediction has become an urgent barrier to be resolved. The iterative update of sequencing technology has opened up an emerging situation in immunotherapy research [4]. The rise of metagenomics and bioinformatics has provided a new perspective on the development of microbiology in tumorigenesis [5][6]. Additionally, more and more evidence supports the important position of the microbiome in the immune-metabolic interaction of cancer, especially in response to blocking immune checkpoints [7][8][9].

2. The Amazing Therapeutic Potential of Cancer Immunotherapy

Reports about ICIs making breakthrough progress in the field of tumor treatment are increasing day by day. Currently, the most widely used ICIs in clinical trials include anti-PD-1/PD-L1 (nivolumab/pembrolizumab/durvalumab/atezolizumab) and anti-CTLA-4 (ipilimumab) [10]. The Topalian team found that nivolumab combines clinical efficacy and high safety in the treatment of various solid tumors such as melanoma [11]. The results showed that patients with advanced melanoma without BRAF mutations had significantly improved overall survival (OS) after receiving nivolumab treatment. Meanwhile, the results of the study were also approved by another phase III randomized double-blind trial [12]. In addition, Takamida et al. reviewed the efficacy of the first-line regimen containing pembrolizumab in patients with metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (tumor proportion score (TPS) ≥ 50%) in the past three years [13]. The study clarified that the first-line pembrolizumab single-agent regimen significantly prolonged the patient's OS and progression-free survival (PFS). Additionally, in the case of similar TPS, pembrolizumab combined with chemotherapy and monotherapy was beneficial to the survival of NSCLC patients [14]. However, another randomized controlled phase 3 trial comparing pembrolizumab with locally advanced NSCLC chemotherapy (KEYNOTE-042) revealed that the OS of the pembrolizumab group was significantly longer than that of the chemotherapy group (p = 0.0018) [15]. Therefore, the important position of pembrolizumab as the first-line standard therapy to treat NSCLC with high PD-L1 expression was affirmed.

Colorectal cancer (CRC) is a highly heterogeneous tumor, and its different subtypes have differentiated responses to immunotherapy [16]. CRC with high microsatellite instability (MSI-H) has high tumor mutational burden (TMB), TH1 immune infiltration, and immune checkpoint gene expression, which would have a positive effect on immunotherapy [17][18]. In MSI-H CRC, higher TMB is the objective reaction of pembrolizumab immunotherapy and the strongest biomarker of PFS [19]. However, this part of the patient accounts for 5% of the transfer of CRC patients. Microsatellite stabilization (MSS) accounts for 95% of patients with metastasis CRC and is resistant to immunotherapy [20]. High TMB MSS CRC patients have reactions to PD-1 inhibitors [21]. In addition, a prospective clinical trial (Keynote-158) found that the high TMB (TMB > 10) can effectively predict the efficacy and prognosis of Pembrolizumab [22]. This phenomenon suggests that high TMB may be used as an indicator of MSS CRC, which is conducive to the patient obtaining immunotherapy benefits. Researchers briefly summarize the application and effect of some ICIS in solid tumors for reference.

Currently, multiple groups of clinical trials provide evidence to support the combination of immunotherapy and chemotherapy for the treatment of a variety of malignancies. NSCLC is a pioneer in trials combining chemotherapy and immunotherapy. After observing that immunotherapy was effective in PD-L1-high (>50%) tumors and in patients treated with platinum chemotherapy, clinicians performed immunotherapy as maintenance in a phase II trial [23]. The results showed that the therapy had a significant effect on adenocarcinoma (HR 0.49; p < 0.001) and squamous cell carcinoma (HR 0.64; p < 0.001) [24]. A phase III clinical trial found that pembrolizumab combined with chemotherapy (paclitaxel/carboplatin/gemcitabine) had a significant benefit in patients with a composite positive score (CPS) ≥ 10 compared with chemotherapy alone (HR 0.65; p = 0.00411) [25]. A meta-analysis of

chemotherapy combined with immunotherapy in metastatic triple-negative breast cancer (mTNBC) revealed that the addition of PD-1/PD-L1 blockade to chemotherapy improved PFS in patients with PD-L1-positive mTNBC [26]. Therefore, immunotherapy has great development space for the original tumor treatment system.

3. Intestinal Microbiota Regulates Pharmacokinetics

Pharmacokinetics refers to the laws of drug absorption, distribution, metabolism, and excretion in the body [27]. Several studies have suggested that the gut microbiota may lead to changes in the chemical modification of medicinal products, resulting in activation, inactivation, or toxicity [28]. However, quantifying microbial intervention on pharmacokinetics remains challenging, especially based on the common basis of drug metabolism of the host and microbiota. Zimmermann M's team combined the genetics of microbial symbiosis with gnotobiotics for the first time [29]. By monitoring the metabolic changes of brivudine (BRV) in mice caused by a single microbially encoded enzyme, they innovatively established a pharmacokinetic model and predicted quantitative microbial contributions to systemic drug metabolism [29]. They compared the serum kinetics of oral BRV in conventional (CV) and germ-free (GF) mice and demonstrated that BRV is converted to hepatotoxic bromoyluracil (BVU) by microbial enzymes, reducing BVU exposure in GF mice [29]. BVU interferes with pyrimidine metabolism in humans by binding to DPD, with lethal consequences in patients receiving chemotherapy with pyrimidine-like drugs such as 5-fluorouracil (5-FU) [30]. In addition, they found that Bacteroides and Oobacteria had the highest metabolic activity to convert BRV to BVU. This provides the microbiome's understanding of drug metabolism and aims to improve the response to drugs in chemotherapy patients. Additionally, they mapped human microbial drug metabolism by measuring the drug-modifying capacity of representative gut bacterial generations and systematically analyzing drug–microbe interactions by identifying drug-metabolizing microbial gene products [31]. Therefore, microbial intervention has a positive strategic effect on chemotherapy and drug metabolism.

4. Microbiota Correlates with Cancer Immunotherapy

The microbiota mainly inhabits the human intestines and maintains the host's metabolism and immune crosstalk [32]. The microbial genome is more than 150 times that of the human body itself, so it is also called the second set of the human genome [33]. It covers a cumulative total of more than 1000 bacterial species, which endows the metagenomics with a common core while maintaining individual differences. Driven by the revolution of high-throughput sequencing technology, microbial research has quickly entered a new era of whole-genome sequencing from laboratory culture [34]. Metagenomics can also be combined with other omics to analyze the metabolism and immune processes of microorganisms, including transcriptomics, metabolomics, and proteomics [35][36]. Surprisingly, the intestinal microbiota has gradually been recognized as being able to intervene effectively in tumor immunotherapy, reduce the incidence of adverse events, and benefit patients [37].

In the early stage, in order to determine whether the microbiome interferes with the therapeutic activity of ICIs, melanoma mice (TAC mice with more severe tumors) carrying different intestinal microbiota but the same genotype from TAC and JAX were used to assess their correlation [38]. The results showed that Bifidobacterium was most

significantly enriched in the feces of JAX mice and had a higher correlation with peripheral and intratumoral specific CD8+ T cell activation. Interestingly, after TAC mice were further transplanted or co-cultured with JAX mouse fecal bacteria, the differences between the two gradually approached [39]. This also directly established the status of the gut microbiome in immunotherapy. In the later stage, after PD-L1 ICIs were combined with mouse fecal suspension, tumor invasion and growth were consistently and significantly slowed, as expected [38].

5. Gut Microbiome Expands Path for Cancer Immunotherapy

In addition, Chaput et al. speculated from the baseline microbiome that the incidence of colitis in patients with metastatic melanoma treated with ipilimumab is regulated by the microbiome [40]. The study prospectively proposed that identifying the attributes of the microbiota is beneficial to avoid and control adverse risks that patients may encounter [40]. According to the RECIST 1.1 standard, patients with different microbiomes can be classified as responders (R) and non-responders (NR) [41]. On this basis, Derosa et al. successfully inoculated feces from R into NR through FMT technology to compensate for the anti-PD-1 immune effect [42][43]. Although the advantages of the microbiome in immunotherapy have become increasingly prominent, there are still challenges in screening out bacterial groups that are specifically enriched for ICIs [44]. With the support of Metatagenomic Shotgun Sequencing and Unbiased Metabolomic Profiling, stool analysis of R and NR is expected to provide clues for the identification of the intestinal microbiota [45].

Although the preclinical mouse model of intestinal microbiota intervention ICIs has been established, there is still a lack of evidence for its application to cancer patients. By analyzing the stool samples of melanoma patients treated with ICIs, Gopalakrishnan and others found significant differences in the diversity and number of intestinal microbiota between responders and non-responders [10]. In particular, the alpha diversity (a statistical method of the distribution and composition of bacteria in the sample) and the relative abundance of Ruminococcaceae ($p <$ 0.01) in the feces of the responders were significantly increased, and the function of effector T cells in the tumor microenvironment (TME) was improved [10]. On the contrary, the feces of non-responders is often accompanied by a lower abundance of bacteria, and there is an enrichment of Bacteroidales, which block lymphatic infiltration and impair tumor immune response.

In an independent cohort study of combined treatment (ipilimumab plus nivolumab) of metastatic melanoma, Frankel et al. reported an increase in the abundance of Faecalibacterium in baseline stool samples of responders and non-responders [7]. The abundance of Faecalibacterium and the longer PFS showed a positive correlation trend [45]. According to the immunophenotype analysis of matched tumors and blood samples of patients in this cohort, the abundance of Faecalibacterium not only has a strong positive correlation with CD8 + T infiltration in the TME but also has a certain correlation with peripheral CD4+/CD8 + T cells [45]. Furthermore, in 32 NSCLC patients, enrichment of Enterococcus faecium also enhanced peripheral CD8+/CD4 + T cell responses and IFN-γ production, prolonging the PFS of R [46].

Coincidentally, by analyzing the stool samples from patients with metastatic melanoma, Matson et al. found that the degree of Bifidobacterium longum, Collinsella aerofaciens, and Enterococcus faecium enrichment in patients with

anti-PD-1 was positively correlated with treatment response and inhibited tumor growth [47]. Additionally, after FMT rebuilds the intestinal environment of sterile mice, tumor control is significantly strengthened. This increased therapeutic effect is mediated by the activation of DCs, which leads to increased initiation and accumulation of CD8 + T cells in TME [48]. This also verifies that the intestinal microbiota from responders is involved in improving immunotherapy or as a candidate biomarker to promote immune surveillance of cancer [49]. Through 16S ribosomal RNA sequencing identification, Sivan et al. found that the effect of oral Bifidobacterium alone can be comparable to anti-PD-1 therapy, and the combined therapy can even completely inhibit tumors [38]. In addition, the metabolites of the microbiota not only reactivate dendritic cells (DCs) but also induce the metabolic reorganization of CD8 + T cells in the TME, providing a basis for the long-term survival of memory cells [50].

When comparing the intestinal microbiota of patients with different malignancies receiving immunotherapy, Routy et al. found that Akkermansia muciniphila (A. muciniphila) was more enriched in the feces of responders (p = 0.007) [43]. Interestingly, two independent teams studying NSCLC and renal cell carcinoma and studying metastatic melanoma also reached similar conclusions, suggesting the possibility of A. muciniphila as a biomarker [51][52]. It is worth mentioning that after co-culture of A. muciniphila with peripheral blood mononuclear cells of responders or non-responders, the effect of responders' CD4+/CD8 + T cells in producing IFN-γ-related memory T cells was significantly stronger than that of non-responders [53]. At the same time, passing A. muciniphila through FMT can re-establish the immune checkpoint blocking effect of non-responders.

In addition, Bacteroidetes are increasingly recognized to be associated with the development and exacerbation of induced colitis [54][55]. In melanoma patients treated with ICIs, the abundance of Bacteroidetes appears to be positively correlated with colitis resistance [56]. Recently, a number of studies proved that different microbial populations excel in optimizing the therapeutic effects of different ICIs, improving the prognosis of patients [57][58].

6. The Clinical Application of Intestinal Microbiota

With the continuous expansion of research data, the gut microbiota provides unprecedented opportunities for the development of immunotherapy-related therapies. Although the mechanism of the gut microbiota in cancer immunotherapy remains to be explored, many cutting-edge studies provide valuable clinical evidence for the gut microbiota with application potential. According to recent clinical studies, researchers use a Sankey diagram to build a very meaningful bridge between ICIs (anti-PD-1/PD-L1 or anti-CTLA-4) and the enrichment of the intestinal microbiota.

Intestinal microbiota optimization and adjuvant immunotherapy have been confirmed, which provides confidence in reducing the complications of cancer immunotherapy [59]. Among them, the most common immune-related adverse event is related to colitis, but the cause is still unknown. Interestingly, colitis was effectively relieved under the intervention of the lactic acid bacteria Lactobacillus reuteri, and the patient's weight loss and inflammation symptoms were significantly improved [60]. In addition, the activation of the protection of Lactobacillus reuteri may be based on the decrease in lymphocyte distribution [61]. The emergence of tumor microecological immunonutrition

further provides an opportunity for the microbiota as a breakthrough in cancer immunotherapy [62]. The ketogenic diet has also been reported to enhance the efficacy of immunotherapy [63].

A number of studies have proposed that adjusting the composition of the gut microbiota can effectively improve immunotherapy, including FMT, dietary intervention, probiotics, or prebiotics [64]. Among them, FMT is gradually recognized as a beneficial clinical intervention. FMT is perfused or orally transplanted into the patient's intestines in the form of bacterial liquid or capsules [65]. At present, FMT has been proven to be the first-line treatment for relapsed/refractory Clostridium difficile infection (CDI) and has been included in the national clinical guidelines [66]. Since microbial research turns to an in-depth mechanism direction, the role of the microbiota and metabolites in the field of inflammatory bowel disease and cancer will undoubtedly be further highlighted [67][68][69]. Certainly, FMT is in its infancy in cancer clinical exploration, but it is a landmark discovery in the field of cancer therapy.

7. The Combination of FMT and Immunotherapy

The combination therapy of FMT and ICIs not only takes into account the curative effect but also guarantees better safety. Baruch et al. performed intestinal microbiota reconstruction in 10 groups of patients with anti-PD-1 refractory metastatic melanoma [70]. After using vancomycin to destroy their own intestinal microbiota for 3 days, the patient rebuilt a new intestinal environment through FMT [71]. After receiving the anti-PD-1 ICIs again, two patients had partial remission, and one patient had complete remission with PFS for more than 6 months. Only some patients experienced discomfort, such as abdominal distension, and no other adverse reactions occurred [72].

Another study also performed FMT and PD-1 monoclonal antibody combination therapy on 15 patients with anti-PD-1 resistant metastatic melanoma [73]. The results showed that six patients responded to anti-PD-1, and only three patients experienced grade 3 adverse events. The study also further clarified that the combination of FMT and anti-PD-1 therapy weakened bone marrow-induced immune suppression, activated CD56 + CD8 + T cells, and downregulated the expression of IL-8 [74]. In contrast, patients with poor intestinal microbiota exhibited weak anti-tumor immunity due to restricted antigen presentation. The latest FMT and immunotherapy-related clinical trials provide a basis for clarifying the involvement of intestinal microbiota in the regulation of ICIs. The clinical trial (NCT03353402) attempts to improve the gut microbiota of melanoma patients who cannot benefit from immunotherapy through FMT. Another clinical trial (NCT05008861) tried to rebuild the gut microbiota in the immunotherapy of non-small cell lung cancer through FMT. The combination of FMT and ICIs will make a greater contribution to the prognosis of patients. In addition, before the combination therapy of FMT and ICIs, the patient must consume antibiotics orally to destroy the harmful intestinal microbiota in the body. According to reports, the vancomycin–neomycin regimen is currently the most effective preparation for treatment [75]. The results of clinical trials and conventional treatment indicate that antibiotic exposure may reduce the OS rate of patients receiving immunotherapy, but the potential intervention is not yet clear [12][13].

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