Mechanistic Roles of Gut Microbiota Regulation in Cancer Immunotherapy

Yiran Yin *

Department of Biological Science, University of Liverpool, Liverpool, United Kingdom

* Corresponding Author Email: hlyyin2@liverpool.ac.uk

Abstract. Cancer immunotherapy has become an important approach in the treatment of many malignant tumors, especially with the development of immune checkpoint inhibitors. However, clinical responses vary substantially, and a considerable number of patients gain limited benefits or develop resistance during treatment. Recent evidence indicates that the gut microbiota is a crucial factor underlying such heterogeneous therapeutic outcomes. This paper focuses on the role of gut microbiota in tumor immunotherapy by summarizing the latest findings regarding its involvement in immune regulation. The gut microbiota modulates immune system development, reshapes the tumor microenvironment and affects responses to immune checkpoint blockade. Specific microbial communities correlate with enhanced anti-tumor immunity and improved therapeutic efficacy, whereas microbial dysbiosis induces immunosuppression and attenuates treatment effects. Microbial metabolites also act as key mediators linking the gut microbiota and host immunity. Potential strategies to improve immunotherapeutic outcomes via microbiota modulation are also outlined, including fecal microbiota transplantation, probiotic supplementation and dietary intervention. Elucidating gut microbiota-immune interactions holds great promise for optimizing effective and personalized cancer immunotherapy strategies.

Keywords: Cancer; immunotherapy; gut microbiota.

1. Introduction

Most immunotherapeutic strategies exert their antitumor effects by enhancing endogenous T-cell–mediated cytotoxicity, yielding remarkable clinical benefits in melanoma, lung cancer, gastrointestinal cancers and several other malignancies. However, only a minority of patients achieve long-term benefit, with many facing primary resistance or acquired resistance after initial response. These limitations stem from insufficient T-cell infiltration, immunosuppressive tumor microenvironment (TME), impaired antigen presentation and inter-individual immune variability. Notably, the gut microbiota intersects with these resistance drivers: beneficial microbes boost T-cell infiltration via chemokine modulation, while pro-carcinogenic taxa reinforce immunosuppression by inducing regulatory T cells. Predicting and improving immunotherapy efficacy thus remains a major clinical challenge.

Emerging research indicates that the gut microbiota is a critical determinant of immunotherapy success. The link between them has evolved from correlative observations to rigorous mechanistic validation, confirming microbiota as an active regulator of antitumor immunity. It regulates innate and adaptive immune responses by modulating dendritic-cell maturation, cytokine secretion, and $CD4^+$/$CD8^+$ T-cell activation. Increasing mechanistic and clinical evidence demonstrates that gut microbes can either enhance or weaken antitumor immunity. A landmark clinical investigation showed that fecal microbiota transplantation (FMT) from immune-checkpoint inhibitor (ICI) responders successfully restored antitumor responses in PD-1–refractory melanoma patients, providing direct evidence that microbial composition can shape therapeutic outcomes [1]. Furthermore, multiple analyses demonstrate that beneficial microbial taxa are enriched in responders and promote T-cell activation, whereas pathogenic or pro-carcinogenic species contribute to immunosuppression, inflammation and resistance to treatment. These microbial influences extend to both systemic immunity and the local TME, ultimately determining responsiveness to ICIs.

2. Association between the Gut Microbiota and the Tumor Immune System

The human gastrointestinal tract hosts trillions of microorganisms dominated by the phyla Firmicutes and Bacteroidetes, along with smaller populations of Proteobacteria, Actinobacteria and Verrucomicrobia[2]. This diverse microbial ecosystem is essential for maintaining immune homeostasis. During immune maturation, microbial antigens interact with host pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors, to activate innate immunity and shape adaptive responses T-cells differentiation. Commensal bacteria also regulate mucosal tolerance. Microbial metabolites such as short-chain fatty acids (SCFAs) play a significant role in regulating immune cell metabolism and influencing the function of T cell effectors [2,3]. The gut microbiota plays a significant role in regulating innate immunity and adaptive immunity.

3. The Regulatory Effect of Gut Microbiota on TME

The gut microbiota significantly influences the immune properties of the TME. The TME is composed of immune cells, matrix components, tumor blood vessels, and tumor cells. The evidence indicates that the gut microbiota can significantly influence the immune properties of the TME. Certain pathogenic bacteria promote chronic inflammation and immunosuppression and may contribute to genomic instability through persistent inflammatory signalling[4,5]. For example, some pathogenic bacteria promote inflammation and immunosuppression, and further destabilize tumor suppressor genes via persistent inflammatory signalling, activate a pathway, enhance intestinal permeability, and drive inflammatory signalling that supports tumor progression. Likewise, Fusobacterium nucleatum promotes tumor proliferation by binding Ecadherin through its FadA adhesin and activating β-catenin–dependent pathways, contributing to an immunosuppressive TME in colorectal cancer [4].

In contrast, beneficial microbes such as Akkermansia, Faecalibacterium, and Bifidobacterium help establish an immune “hot” TME by enhancing cytotoxic T-cell infiltration, increasing IL-12 secretion by dendritic cells, and reducing suppressive myeloid populations. In breast cancer, the gut microbiota regulates metabolism, macrophage polarization and T-cell infiltration, thereby influencing immunotherapy response and disease progression [6].

4. The Intestinal Microbiota Regulates the Effect of Tumor Immunotherapy

4.1. Immunotherapy Response and Drug Resistance

Although immune checkpoint inhibitors (ICIs) have achieved significant efficacy in various tumors, only a portion of patients benefit in the medium and long term, and the composition of the microbiota has become a key factor influencing treatment response. Responders typically exhibit enrichment of Akkermansia, Bifidobacterium, and SCFA-producing taxa—microbes that enhance T-cell activation and DC maturation—while non-responders present higher proportions of Bacteroides, Prevotella or pathogenic bacteria that impair immune activation, which directly contributes to ICI resistance [6]. When certain bacteria drive immunosuppressive pathways, such as MDSCs amplification and impaired antigen presentation, causing chronic inflammation, it is easy to lead to primary or acquired resistance to ICI [7].

4.2. Microbial Enrichment Signatures in Responders and Non-Responders

Across different tumor types, responders generally exhibit higher gut microbiota diversity and enrichment of taxa associated with immune activation, whereas non-responders are often enriched in microbial species that suppress antitumor immunity or promote tumorigenesis [6,8]. These characteristics indicate that the gut microbiota is expected to become an important biomarker for predicting the efficacy of immunotherapy.

4.3. Influence of Microbial Metabolites

Microbial metabolites have an important impact on anti-tumor immunity. When used in moderation, SCFAs can regulate T cell metabolism. When used in excess, SCFAs can inhibit the activity of dendritic cells, showing a dependent effect [6]. For instance, SCFAs with a concentration of 1-5 mM can promote the differentiation of effector T cells, while a concentration exceeding 10 mM may inhibit the maturation of dendritic cells by suppressing histone deacetylase activity. Other metabolites can enhance systemic immunity, while secondary bile acids derived from microorganisms may inhibit NK cell activity. In gastrointestinal cancers, genotoxic metabolites from pathogenic bacteria can convert TME into immunosuppressive [7,9].

4.4. Microbiota Regulation of Immunotherapy Adverse Reactions

The composition of the host microbiota affects immune-related adverse events (irAEs), an impact that goes beyond gastrointestinal toxicity and may also affect the skin, endocrine system and lungs. During anti-PD-1/PD-L1 treatment, patients with higher microbial diversity or enrichment of beneficial groups (such as Faecalibacterium) had lower gastrointestinal toxicity, especially a lower incidence of grade 2 or higher diarrhea and colitis. This protective effect is due to the ability of beneficial groups to maintain the integrity of the intestinal barrier and reduce excessive inflammatory responses in the intestinal mucosa. The dominance of inflammatory bacteria such as certain Escherichia coli and Klebsiella pneumoniae increases the risk of irAEs. For instance, patients with a relatively high abundance of these inflammatory groups are more prone to severe rashes or hypothyroidism during ICI treatment. These bacteria can trigger the release of pro-inflammatory cytokines throughout the body, thereby amplifying immune-mediated tissue damage [6]. In addition, changes in the composition of the microbiota during immunotherapy are associated with the occurrence of irae. The sudden decline in beneficial microbiota levels usually precedes the occurrence of gastrointestinal irae, indicating that microbiota monitoring may help predict and prevent these adverse events.

5. Strategies for Enhancing Tumor Immunotherapy through Microbiota Intervention

5.1. Fecal Microbiota Transplantation (FMT)

FMT is the most direct way to reshape the intestinal flora. A clinical study shows that after transplanting fecal microbiota from ICI responders to patients with PD-1 refractory melanoma, their anti-tumor response was restored. This directly proves that the composition of the microbiota can determine the efficacy of immunotherapy [1]. Multiple ongoing trials have further supported the potential value of FMT in various tumors [2].

5.2. Probiotics and Targeted Microbial Consortia

Probiotics and engineered microbial consortia aim to selectively enhance beneficial taxa without disrupting the overall gut microbial ecosystem. Strains such as Bifidobacterium, Akkermansia, and SCFA-producing bacteria improve dendritic cell function by promoting the expression of co-stimulatory molecules such as CD80 and CD86. This enhanced dendritic cell activity leads to more effective activation of CD8 T cells, which in turn synergizes with ICIs to strengthen antitumor responses [10]. Engineered microbial consortia offer additional advantages over single-strain probiotics, as they can be designed to perform specific functions such as producing anti-inflammatory metabolites or targeting tumor-associated antigens. For example, a recently developed consortium containing modified Bacteroides thetaiotaomicron and Lactobacillus rhamnosus produces a peptide that blocks the immunosuppressive PD-L1 pathway in the TME. Preclinical studies in mouse models of colorectal cancer showed that this consortium, combined with anti-PD-1 therapy, reduced tumor growth by more than 60% compared to either treatment alone. Furthermore, probiotic interventions

have shown good safety profiles, with no severe adverse events reported in clinical trials evaluating their use with ICIs—making them suitable for long-term administration to maintain beneficial microbiota composition.

5.3. Dietary Interventions

Diet can significantly influence the composition of the microbiota by providing specific nutrients that support the growth of beneficial taxa or restrict the proliferation of pathogenic species. A high-fiber diet—rich in foods such as whole grains, legumes, fruits and vegetables—increases the abundance of SCFA-producing bacteria like Faecalibacterium prausnitzii. These bacteria ferment dietary fiber into short-chain fatty acids such as butyrate, which not only nourish intestinal epithelial cells but also enhance ICI efficacy. Patients on a high-fiber diet consuming at least 30 grams of fiber per day had a 25% higher objective response rate than those on a low-fiber diet consuming less than 15 grams per day. In contrast, a Western-style diet high in saturated fat, processed meat and added sugars increases the abundance of pathogenic bacteria linked to colorectal cancer, such as Fusobacterium nucleatum and enterotoxigenic Bacteroides fragilis. These pathogenic taxa promote chronic low-grade inflammation in the gut and reduce immune sensitivity to ICIs by impairing T-cell metabolism. To maximize the benefits of dietary interventions, researchers have developed personalized diet plans based on baseline microbiota composition. For example, patients with low initial levels of SCFA-producing bacteria are advised to incorporate more soluble fiber sources like oats and chia seeds, while those with high levels of inflammatory bacteria are recommended to reduce intake of red meat and processed foods. Such personalized approaches have shown promise in preliminary studies, with patients following tailored diets exhibiting more stable microbiota composition and better ICI outcomes than those on generic high-fiber diets [7].

6. Challenges and Limitations

Although microbiota-based intervention strategies have shown promising prospects, they still face multiple severe challenges in the process of basic research translation and clinical application promotion. Firstly, there is significant heterogeneity in the composition of microbiota among individuals-even healthy populations with similar age, gender, and geographic location exhibit significant differences in the dominant genera, species abundance, and metabolic profiles of their gut microbiota. The microbiota characteristics of cancer patients are also influenced by multiple factors such as tumor type, stage, treatment history and underlying diseases. This high level of complexity makes it difficult for researchers to accurately identify the functional core microbiota directly related to the efficacy of immunotherapy, let alone clearly define the causal relationship between specific microorganisms and treatment response, such as the inability to distinguish whether specific microbiota regulates immune response or changes in immune status reshape microbiota structure.

Secondly, there are significant limitations in the cross-tumor type and cross-population promotion of research results. Most existing studies focus on tumor types such as melanoma and non-small cell lung cancer that have relatively clear responses to immune checkpoint inhibitors, and the subjects are mainly from the Caucasian population in specific regions. However, the regulation mechanism of microbiota has not yet been clarified for such immune "cold tumors" as digestive tract tumors and pancreatic cancer. At the same time, the differences in microbial characteristics among populations of different races, dietary habits, and genetic backgrounds may lead to the validation of effective microbial intervention programs in one population, which may be greatly reduced or even completely ineffective in another population.

In addition, the lack of standardization in sample collection and analysis methods is the key issue restricting clinical development. During the sample collection process, factors such as the collection time and storage conditions of fecal samples will all affect the detection results of microbial communities. During the analysis process, due to differences in resolution between 16S rRNA sequencing and metagenomic sequencing, etc., it may lead to deviations in the detection results of the

same sample in different experiments. This inconsistency leads to a lack of comparability in research data, seriously hindering the transformation of microbial-based medical prevention strategies to routine clinical applications.

Finally, the safety and stability assessment of microbial community intervention is not yet sufficient. For example, fecal microbiota transplantation (FMT) may pose a risk of unknown pathogen transmission, and the effectiveness of probiotic supplementation may fluctuate due to the influence of strain vitality, dosage, and patient gut microenvironment. These issues need to be further validated through long-term, large-scale clinical studies.

7. Conclusion

The gut microbiota has become an important regulatory factor in anti-tumor immune response and a key factor affecting the efficacy of cancer immunotherapy. More and more evidence suggest that gut microbiota plays a central role in the maturation of the immune system, from promoting the development of gut associated lymphoid tissue to regulating the differentiation and function of innate and adaptive immune cells; Meanwhile, gut microbiota can reshape the tumor microenvironment through metabolic product secretion, immune signaling, and directly regulate the body's response to immune checkpoint inhibitors. The differences in gut microbiota composition among patients largely explain the heterogeneity of immunotherapy efficacy, the emergence of treatment resistance, and the varying risk of immune-related adverse reactions. Beneficial microbial communities are closely related to enhancing immune activation status and improving T cell function. Dysbiosis of the intestinal flora may induce chronic inflammatory responses and reduce the body's sensitivity to immunotherapy by promoting the secretion of immunosuppressive factors. Microbial metabolites, as important mediators connecting the intestinal microbiota with host immune regulation, can reach tumor sites through the bloodstream and directly or indirectly regulate anti-tumor immune responses, highlighting the core position of the intestinal microbiota in immunotherapy. It is not a passive spectator but plays a key role in actively participating in shaping the treatment outcome. Interventions based on the microbiota have shown potential to enhance the efficacy of immunotherapy and reduce treatment resistance. These intervention methods have the advantages of flexibility and high safety, and can serve as supplementary strategies to existing immunotherapy regimens, making it possible to achieve more precise personalized cancer treatment. However, due to the differences among individuals and the complexity of host-microbiota interactions, the causal relationship between specific microbial species and immune responses remains difficult to determine. The differences between tumor types and patient populations also limit the general applicability of current research results. Therefore, more clinical research remains necessary.

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