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THE INTERPLAY BETWEEN GUT MICROBIOTA AND CANCER IMMUNOTHERAPY

Nebin Sajeer*[1], Sandra Prasanth[2], Anjitha B. S.[3], Jessica Sanil[4], Devananda H.[5] and Dr. Aneeta Toms[6]

[1,2,3,4,5]PharmD Intern, The Dale View College of Pharmacy and Research Centre Punalal Po, Trivandrum, Kerala, India.
[6]Associate Professor, The Dale View College of Pharmacy and Research Centre, Trivandrum, Kerala, India.

***Corresponding Author: Nebin Sajeer**

PharmD Intern, The Dale View College of Pharmacy and Research Centre Punalal Po, Trivandrum, Kerala, India.

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ABSTRACT

The gut microbiota represents the body's most extensive and dynamic microbial ecosystem, playing a fundamental role in regulating immune function. Extensive research has demonstrated that both the composition of the gut microbiota and the metabolites it produces contribute significantly to the modulation of host immune responses. Immune checkpoint inhibitors (ICIs) have emerged as a transformative class of drugs in oncology, offering improved survival for patients with various advanced malignancies. Nevertheless, a substantial proportion of individuals do not respond favorably to these therapies. Current strategies to manipulate the gut microbiome—such as fecal microbiota transplantation (FMT), dietary interventions, and the use of prebiotics—have shown potential in modifying the immune landscape. This review explores the potential of leveraging gut microbiota modulation to enhance the therapeutic efficacy of cancer immunotherapy and addresses how microbiome-focused interventions might help overcome current limitations in ICI response.

KEYWORDS: Gut Microbiota, Immune Checkpoint Inhibitors (ICIs), Cancer Immunotherapy, Microbiome Modulation, Biomarkers of Treatment Response.

INTRODUCTION

Recent research has uncovered a fascinating dual role of certain bacteria in cancer. While some microbes stimulate the immune system to target and destroy tumor cells, others create an immunosuppressive environment that allows cancer to grow unchecked.[1] Immune checkpoint inhibitors have emerged as a key advancement in the treatment of various aggressive cancers, offering the potential to greatly extend survival for many patients. Despite their promise, a significant portion of individuals fails to respond to these therapies, highlighting the variability in treatment outcomes and the need for deeper understanding of resistance mechanisms. Increasingly, scientists are recognizing that the success and side effects of cancer immunotherapy may be closely tied to the balance and makeup of the gut microbiome.[2] The influence of the intestinal microbiota on tumors runs through all stages of occurrence, development, and treatment. This review will focus on the interaction between the gut microbiota and tumor immunotherapy, in order to provide new ideas for optimizing tumor immunotherapy.[3]

GUT MICROBIOTA

The gut microbiota forms a complex internal ecosystem made up of over 100 trillion microbes—including bacteria, fungi, and viruses—that live in harmony with the human host. Owing to its profound influence on our physiology and health, it's often referred to as the body's "second genome," highlighting its critical role in shaping human biology.[4] Gut microorganisms can generally be grouped into three main types based on their behavior and impact on the body: beneficial bacteria, opportunistic pathogens, and harmful microbes. Friendly strains like Bacteroidetes, Clostridium, Bifidobacterium, and Lactobacillus play a vital role in maintaining health by aiding digestion, producing vitamins, regulating cholesterol, and strengthening immune function. In contrast, certain microbes that are typically harmless under stable conditions can become problematic when the gut environment is disrupted, potentially leading to disease and inflammation.[5] However, when the immune system is compromised or the body is in a weakened state, some of these ordinarily harmless microbes—such as Escherichia coli and Enterococcus—can multiply excessively or migrate beyond the gut, causing tissue damage and intestinal complications. In contrast, pathogenic bacteria are those that do not naturally reside in the gut and are typically introduced from external sources, often leading to infection and disease upon colonization.

GUT MICROBIOTA AND IMMUNE SYSTEM

The composition of gut microbiota varies greatly from person to person, even among individuals in good health.[6] These microbial communities inhabit the intestinal epithelium, where they exist in a mutually beneficial relationship with the host. This intricate microbial network is vital for maintaining physiological balance, and its disturbance has been linked to a range of pathological conditions, including chronic inflammation, autoimmune disorders, cardiovascular disease, and various forms of cancer.[7,8] Research over recent years has revealed that these resident microbes can exert both protective and promotive effects on cancer development, influencing its onset, progression, and the spread of malignant cells.

Evidence suggests that lowering the overall bacterial presence in the gut can significantly hinder the growth of colorectal tumors.[9] Beyond well-known cancer-promoting microbes, imbalances in the gut microbiome—a condition known as dysbiosis—have emerged as a critical factor in the early stages of cancer development.[10] The pathways through which gut microbes contribute to tumor formation are multifaceted, involving the release of harmful metabolic byproducts, the creation of a pro-inflammatory environment, and the dampening of the body's natural immune defenses against tumors. These processes can result in DNA damage, genomic instability, and allow cancer cells to evade immune detection.[11,12] More recent investigations have also highlighted alternative routes, such as hormonal modulation and interactions via the gut-brain axis, providing insight into how gut microbes might trigger abnormal cell growth even in organs far removed from the digestive system.

Building on this intricate relationship, it becomes increasingly evident that the gut microbiota does not function in isolation but is in constant dialogue with the host immune system.[13] Microbial byproducts, such as short-chain fatty acids (SCFAs), indoles, and secondary bile acids, serve as signaling molecules that can influence immune cell behavior, modulate inflammatory pathways, and maintain epithelial homeostasis.[14] These metabolites can enhance regulatory T-cell function, support the integrity of mucosal barriers, and help suppress excessive immune activation that could otherwise lead to tissue damage. Conversely, a shift in microbial composition or metabolite production—whether due to aging, diet, antibiotic use, or disease—can disrupt this balance, tipping the system toward chronic inflammation or immune dysfunction. This dynamic interplay suggests that the gut microbiome is both a target and a regulator of immune health, with its composition and activity potentially serving as biomarkers or therapeutic targets in age-related and immune-mediated disorders.[15,16]

GUT MICROBIOTA AND IMMUNOTHERAPY

The therapeutic landscape of cancer has been transformed by immunotherapies, which work by re-engaging the immune system to recognize and eliminate tumor cells. These strategies aim to restore the disrupted tumor–immune cycle and boost the host's antitumor immune responses. Established immunotherapeutic approaches include immune checkpoint blockade (ICB), monoclonal antibodies, cancer vaccines, adoptive T-cell transfer, immune-modulating agents, and small-molecule inhibitors. Among them, ICB has shown substantial clinical promise but is marked by variable effectiveness across patients.[17] In recent years, accumulating evidence has pointed to the gut microbiome as a significant factor influencing patient responses to immunotherapy. Distinct microbial patterns, identified through fecal or gut microbiome profiling, have been associated with treatment efficacy, patient prognosis, and even potential adverse effects.[18] These insights suggest that the gut microbiota may serve as a biomarker for predicting immunotherapy outcomes. More importantly, intentional modulation of the gut ecosystem—through probiotics, dietary interventions, or microbial transplantation—offers a novel route to enhance therapeutic benefit or mitigate toxicity. Targeting specific microbial species to fine-tune the immune landscape thus represents an emerging and promising strategy to improve the precision and success of cancer immunotherapy.[19]

One of the earliest studies highlighting the connection between gut microbiota and cancer immunotherapy was conducted by Zitvogel and colleagues in 2015.[20] Their work focused on how commensal bacteria influence the therapeutic effect of anti-Cytotoxic T-lymphocyte Associated Protein 4 (CTLA-4) antibody treatment. Using murine models raised under different microbiological conditions—germ-free (GF), specific pathogen-free (SPF), and antibiotic-treated—they observed that the absence of gut microbes significantly reduced the efficacy of anti-CTLA-4 therapy.[21] Conversely, restoring the microbiota, particularly with specific bacterial species from the Bacteroidales (Bacteroidetes phylum) and Burkholderiales (Proteobacteria phylum) orders, markedly improved treatment outcomes. Beyond enhancing therapeutic response, these microbial species also appeared to mitigate one of the major immune-related adverse events associated with CTLA-4 blockade: colitis. In fact, mice colonized with these strains showed reduced intestinal inflammation on histological examination. Some clinical evidence also supports the idea that Bacteroidales species are protective against colitis in patients receiving anti-CTLA-4 therapy. However, the relationship is not straightforward—other studies have linked certain members of this same bacterial order with gastrointestinal disorders such as colitis and Crohn's disease.[22,23] These inconsistencies point to important confounding factors in microbiome research. Variables such as antibiotic resistance, undefined baseline microbial populations in treated mice, and inter-individual differences make it challenging to interpret results uniformly. Moreover, while mouse models are invaluable for controlled experimental work, translating findings to human systems is not always direct or reliable. Fundamental differences exist between murine and human gastrointestinal anatomy and microbial composition—up to 85% of bacterial species in mice are not present in humans. If future clinical studies confirm that administering live bacterial strains alongside CTLA-4 blockade enhances treatment response, then several factors must be carefully evaluated.[24,25] These include patient-specific dietary influences, microbial community shifts, and competitive dynamics between introduced bacteria and native microbiota—all of which can impact therapeutic success. Intriguingly, in patients with metastatic melanoma (MM) or non-small cell lung cancer (NSCLC), anti-CTLA-4 therapy itself was found to alter microbial community structure, favoring the growth of certain species at the expense of others.[26] This suggests that immune modulation may reciprocally influence gut microbiota, highlighting a bidirectional relationship that could be central to improving immunotherapeutic strategies.

GUT MICROBIOTA AS A BIOMARKER FOR IMMUNOTHERAPY RESPONSE

Emerging evidence has highlighted the potential of gut microbiota profiling as a non-invasive tool to predict patient responses to immune checkpoint inhibitors (ICIs). Distinct microbial signatures have been observed in individuals who respond to immunotherapy compared to those who do not[10], suggesting that both the composition and metabolic activity of the gut microbiome may serve as predictive indicators of clinical outcomes. In recent years, numerous studies have focused on leveraging gut microbiota as a biomarker to not only distinguish responders from nonresponders but also to forecast the likelihood and severity of immune-related adverse events with minimal invasiveness.

Specific microbial taxa have been consistently associated with improved outcomes in patients receiving ICIs such as PD-1, PD-L1, and CTLA-4 inhibitors. For example, enrichment of *Akkermansia muciniphila*[27], *Bifidobacterium longum*[24], *Bacteroides fragilis*[28], and members of the *Ruminococcaceae* family[29] correlates with enhanced therapeutic efficacy and favorable prognosis. In contrast, a higher relative abundance of species such as *Roseburia intestinalis* and *Bacteroides thetaiotaomicron*[30] has been linked to reduced responsiveness to immunotherapy.

Beyond checkpoint inhibitors, microbiome composition may also influence the success of cell-based therapies. In patients undergoing anti-CD19 CAR T-cell therapy for large B-cell lymphoma, greater bacterial genetic diversity in the gut was associated with improved treatment outcomes. Moreover, metabolic signatures derived from gut bacteria have shown potential as additional biomarkers. For instance, long-term CAR-T responders exhibited enhanced pathways for peptidoglycan synthesis, while increased activity in the nonoxidative branch of the pentose phosphate pathway was linked to a higher risk of therapy-induced toxicity.[31]

Given the multifaceted role of the gut microbiome in shaping immune responses, future predictive models may need to integrate multiple layers of biological data. A comprehensive framework that includes microbial composition, metabolite profiles, tumor-specific genetic alterations, patient age, underlying comorbidities, and germline variations could improve the precision of immunotherapy response prediction. Such an integrative approach would mark a significant advancement toward truly personalized cancer immunotherapy.

CONCLUSION

The gut microbiota acts as a crucial link between multiple physiological systems—including the gut, brain, spleen, and immune system—playing a central role in maintaining systemic homeostasis. Disruption in the balance of this microbial community, particularly the overgrowth of harmful or less beneficial strains, has been associated with the development of both intestinal and extraintestinal cancers. Additionally, such dysbiosis can impair anticancer immune responses and contribute to the formation of an immunosuppressive tumor microenvironment (TME).

A growing body of research has shown that variations in the diversity and composition of the gut microbiome correlate strongly with the effectiveness of immunotherapy and the likelihood of immune-related adverse events (irAEs). These findings underscore the potential of using microbiota profiles as predictive biomarkers for immunotherapy response, and further support the strategy of targeting the microbiome—either as a standalone therapeutic or in combination with immunotherapy.

As this field advances, there is increasing emphasis on the need to develop targeted, safe, and effective methods for reshaping the gut microbiota in cancer patients. The goal is to enrich populations of beneficial commensal bacteria that support antitumor immunity and improve treatment outcomes. This will require deeper investigation into the specific strains that confer immunological benefit, especially across different cancer types. Additionally, tracking how the microbiota evolves over the course of treatment may offer insight into resistance mechanisms and response durability.

Looking ahead, future research should focus on the complex, bidirectional relationship between gut microbes and novel forms of immunotherapy. Deciphering these interactions will be key to designing next-generation interventions that incorporate microbiota modulation as a core element of cancer care.

REFERENCES

1. Wu M, Bai J, Ma C, Wei J, Du XJJoIR. The role of gut microbiota in tumor immunotherapy, 2021; 2021(1): 5061570.

2. Xu X, Ying JJFiM. Gut microbiota and immunotherapy. 2022; 13: 945887.
3. Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA, Knight RJS. The microbiome and human cancer, 2021; 371(6536): eabc4552.
4. Chen Y-Z, Yuan M-Y, Chen YL, Zhang X, Xu X-T, Liu S-L, et al. The gut microbiota and traditional Chinese medicine: A new clinical frontier on cancer, 2021; 22(11): 1222-31.
5. Blaser MJ, Falkow SJNRM. What are the consequences of the disappearing human microbiota?, 2009; 7(12): 887-94.
6. Curtis H, Blaser MJ, Dirk G, Kota KC, Rob K, Liu B, et al. Structure, function and diversity of the healthy human microbiome, 2012; 486(7402): 207-14.
7. Gomaa EZJAVL. Human gut microbiota/microbiome in health and diseases: a review, 2020; 113(12): 2019-40.
8. Chen AT, Zhang J, Zhang YJI. Gut microbiota in heart failure and related interventions, 2023; 2(3): e125.
9. Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai D, et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer, 2017; 358(6369): 1443-8.
10. Pinato DJJEU. Antibiotic-induced Dysbiosis as a Putative Actionable Driver of Cancer Immunity in Renal Cell Carcinoma, 2020; 78(2): 207-8.
11. Gur C, Ibrahim Y, Isaacson B, Yamin R, Abed J, Gamliel M, et al. Binding of the Fap2 protein of Fusobacterium nucleatum to human inhibitory receptor TIGIT protects tumors from immune cell attack, 2015; 42(2): 344-55.
12. Louis P, Hold GL, Flint HJJNrm. The gut microbiota, bacterial metabolites and colorectal cancer, 2014; 12(10): 661-72.
13. Majumdar S, Ruiz DZ, Wu W-J, Orozco S, Bettini M, Diehl G, et al. Regulation of thymic T-cell development by intestinal microbiota, 2020; 204(1): 84.5-.5.
14. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, et al. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases, 2019; 7(1): 14.
15. Xu Y, Wang Y, Li H, Dai Y, Chen D, Wang M, et al. Altered fecal microbiota composition in older adults with frailty, 2021; 11: 696186.
16. Sankaran-Walters S, Hart R, Dills CJFiM. Guardians of the gut: enteric defensins, 2017; 8: 647.
17. Brennan CA, Garrett WSJArom. Gut microbiota, inflammation, and colorectal cancer, 2016; 70(1): 395-411.
18. Nakatsu G, Andreeva N, MacDonald MH, Garrett WSJNm. Interactions between diet and gut microbiota in cancer, 2024; 9(7): 1644-54.
19. Ma W, Mao Q, Xia W, Dong G, Yu C, Jiang FJFim. Gut microbiota shapes the efficiency of cancer therapy, 2019; 10: 1050.
20. Neut C, Bulois P, Desreumaux P, Membreé J-M, Lederman E, Gambiez L, et al. Changes in the bacterial flora of the neoterminal ileum after ileocolonic resection for Crohn's disease, 2002; 97(4): 939-46.
21. Lundberg R, Toft MF, August B, Hansen AK, Hansen CHJGm. Antibiotic-treated versus germ-free rodents for microbiota transplantation studies, 2016; 7(1): 68-74.
22. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JIJPotNAoS. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice, 2007; 104(3): 979-84.
23. Wiles TJ, Jemielita M, Baker RP, Schlomann BH, Logan SL, Ganz J, et al. Host gut motility promotes competitive exclusion within a model intestinal microbiota, 2016; 14(7): e1002517.
24. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti–PD-L1 efficacy, 2015; 350(6264): 1084-9.
25. Buchbinder EI, Desai AJAjoco. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition, 2016; 39(1): 98-106.
26. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients, 2018; 359(6371): 97-103.
27. Routy B, Le Chatelier E, Derosa L, Duong CP, Alou MT, Daillère R, et al. Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors, 2018; 359(6371): 91-7.
28. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota, 2015; 350(6264): 1079-84.
29. Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab, 2017; 28(6): 1368-79.
30. Gong J, Chehrazi-Raffle A, Placencio-Hickok V, Guan M, Hendifar A, Salgia RJC, et al. The gut microbiome and response to immune checkpoint inhibitors: preclinical and clinical strategies, 2019; 8(1): e9.
31. Schubert M-L, Rohrbach R, Schmitt M, Stein-Thoeringer CKJFii. The potential role of the intestinal micromilieu and individual microbes in the immunobiology of chimeric antigen receptor T-cell therapy, 2021; 12: 670286.