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NUTRITION GUT MICROBIOME & PROBIOTICS

THE TRIPLE CONNECTION



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CHAPTER

Interplay between Gut Microbiome and Immune System: Implications in Cancer Immunotherapy

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INTRODUCTION

Immune checkpoint inhibitors (ICIs) have reshaped cancer treatment, significantly improving survival across several malignancies. Moreover, immunotherapy unlike traditional therapies offers a tolerable safety profile and the potential for long-term remission through the generation of immunological memory (Shoji et al., 2022). Moreover, its broad applicability across diverse patient populations further underscores its transformative impact. Despite all the advantages of immunotherapy in cancer treatment, not all patients experience the same level of response. So, there should be some availability of the factors which could help to predict the response to therapy to save the time and money. Factors such as tumor microenvironment (TME) and genetic variation play a significant role in predicting response to immunotherapy. Another critical factor which could help in predicting response is gut microbiota composition, as certain bacterial profiles are linked to responses (Del Giudice et al., 2024). The complex community of microorganism residing in the gut affects overall health. Although human digestive tract comprises trillions of bacteria, viruses, fungi, and many other microorganisms which influences the biological function such as digestion, metabolism, and immune system regulation. Moreover, in a healthy immune system, on the other hand, unstable dysbiosis may lead to metabolic disorders, inflammatory conditions, and many more (Yi, Qin, et al., 2018). This connection highlights the potential of the gut microbiome as a crucial element in predicting and optimizing responses to immunotherapy, offering new opportunities for improving treatment outcomes in cancer (Yi, Yu, et al., 2018).

Moreover, the understanding of relationship between the gut microbiota and immunotherapy in cancer could help clinicians to predict which patients are more prone to benefit from immunotherapy (Chau et al., 2021). Microbiome profiling of patients could lead to more effective and personalized therapy. Furthermore, modification in gut microbiome, such as dietary changes, probiotics, or prebiotics, could help to improve the efficacy of immunotherapy. By examining the connection between gut microbiota composition with treatment efficacy, we aim to highlight how this relationship could lead to more effective cancer therapies. Understanding the gut microbiome and its influence on immune responses could offer new

strategies for optimizing immunotherapy outcomes and improving patient care in various malignancies.

GUT MICROBIOME AND HOST IMMUNITY

The relationship between the gut microbiome and the host immune system is a bidirectional interaction that evolves throughout life. The immune system is shaped and regulated by the gut microbiome, in turn, influences the composition and balance of the gut microbiota, maintaining gut homeostasis. Disruptions or imbalances in this delicate equilibrium can lead to the development of various pathological conditions, including immune-related disorders and cancer.

The Gut Microbiome and Innate Immunity

The first interaction of microbial invasion is by the innate immune system of the body. Pattern recognition receptors (PRRs) are the germline-coded receptors which identify the microbial-associated components such as flagellin, lipopolysaccharides, and distinct nucleic structures. These are known as pathogen-associated molecular patterns (PAMPs). The identification of PAMPs by PRRs triggers the activation of inflammatory responses and the broader immune system, including the recruitment and activation of B and T cells (Deluce, Maleki Vareki, and Fernandes 2022).

GUT MICROBIOME AND ADAPTIVE IMMUNITY

The lymphoid tissues found in the gut consist of lamina propria and Peyer's patches which are a major part of the immune system. PRRs are recognized within these tissues either on the surface or intracellularly which leads to the maturation of dendritic cells and also naïve B and T cells. This process effectively bridges innate and adaptive immunity. Bacterial antigens are captured either by dendritic cells themselves or via dendritic membrane extensions between epithelial cells or indirectly through M cells, which transport antigens intact to dendritic cells and macrophages via transcytosis. Once naïve T and B cells are activated, then they are differentiated into T regulatory (Treg) cells, effector T cells, and Th17 cells. These immune cells migrate from the lymphoid tissue to mesenteric lymph nodes and eventually enter peripheral blood through the thoracic duct, thereby contributing to systemic immunity. Moreover, Th17 cells are a specialized subset of CD4+ T helper cells that plays crucial roles in host defense and autoimmune diseases by producing proinflammatory cytokines such as IL-17 and IL-22 (Routy et al., 2024).

The lamina propria and Peyer's patches also host macrophages, which are potent immunomodulatory effectors. Moreover, Treg and Th17 cells facilitate class switching in B cells, leading to secretory IgA (SIgA) production. SIgA coats commensal bacteria and soluble antigens which prevent their adhesion

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to intestinal epithelial cells and limit their penetration into the lamina propria. This SIgA-mediated mechanism helps maintain the mutualism between the host and the beneficial microbiome. And it also supports the enhancement of the mucosal barrier against infectious breaches (Hayase and Jenq 2021).

GUT MICROBIOME AND TUMOR MICROENVIRONMENT

Disruption of the gut microbiota can compromise the intestinal barrier, allowing microbial and metabolite leakage. This leakage can result in chronic inflammation, lipid metabolism disturbances, impaired myeloid cell function, and unchecked cellular growth, all of which contribute to tumor development.

Moreover, PAMPs, the microbial molecules, can cross the mucosal barrier, enter circulation, and reach lymph nodes or tumors, where they trigger strong immune responses. However, antigen cross-reactivity has emerged as a concept for enhancing antitumor immunity. Cross-reactive T cells activate against bacterial antigens and may assist in antitumor responses either via CD4+ T cell help or direct tumor cell killing by CD8+ T cells. (Katayama et al., 2019).

Gut bacteria may also modulate antitumor immunity by inducing immunomodulatory cytokines (e.g., TNF-α, IL-12, and IL-10) released by host epithelial or immune cells. These cytokines circulate systemically, altering the activation threshold of immune subsets within the TME and enhancing adaptive immune responses (Luu et al., 2023).

Additionally, the gut microbiota influences antitumor immunity by producing metabolites that enter host circulation. Short-chain fatty acids (SCFAs), for instance, regulate macrophage and dendritic cell functions, activate Treg cells (anti-inflammatory) or Th1 and Th17 cells (proinflammatory), and promote IgA secretion by plasma cells. These actions impact both the TME and tumor-draining lymph nodes (TdLNs), which highlights the multitasked role of the gut microbiome in shaping antitumor immunity.

IMPACT OF GUT MICROBIOME IN ASSOCIATION WITH IMMUNE CHECKPOINT INHIBITOR THERAPY IN CANCER

A growing body of research highlights the connection between the gut microbiome and the safety and efficacy of ICI-based immunotherapy in cancer patients. Pitt et al discovered that tumors in antibiotic-treated mice did not respond to anti-CTLA-4 therapy, and they identified *Bacteroides fragilis* as critical for the antitumor effect of anti-CTLA-4 (Pitt et al., 2017). Their study showed that the immunization with its derived polysaccharides of *B. fragillis* or adoptive transfer of *B. fragilis*-specific T-cells enhanced the therapeutic response. Furthermore, fecal microbiota transplantation (FMT) from melanoma patients with high *Bacteroides* abundance also

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enriched *B. fragilis* in recipient mice, which was associated with reduced tumor size following CTLA-4 blockade (Peters et al., 2019). In the same year, Sivan et al demonstrated that melanoma growth differed in mice with distinct gut microbiome compositions (Sivan et al., 2015). They showed that oral administration of feces from anti-PD-L1 therapy responders or *Bifidobacterium* enhanced the response of nonresponder mice to anti-PD-L1 therapy by boosting dendritic cell activity, promoting CD8+ T-cell priming, and increasing T-cell infiltration in tumors.

Subsequent studies in 2016 and 2017 further explored gut microbiome compositions in cancer patients, linking specific microbiota to enhanced immune responses and reduced colitis induced by ICIs. Notably, Dubin et al., found that the presence of *Bacteroidetes* is related with resistance to colitis due to ICI (Dubin et al., 2016), while Chaput et al., identified bacterial species such as *Bacteroides caccae* and *Faecalibacterium prausnitzii* as key factors for ICI response (Chaput et al., 2017). Landmark studies in 2018, such as those by Routy et al., Matson et al., and Gopalakrishnan et al., established direct links between gut microbiome composition and ICI efficacy, identifying species such as *Akkermansia muciniphila* and *Bifidobacterium longum* as potential biomarkers for ICI response (Routy et al., 2018, Matson et al., 2018, and Gopalakrishnan et al., 2018).

Routy et al., demonstrated that antibiotics disrupt gut microbiome health and reduce the benefits of ICIs, particularly in patients with advanced renal cell carcinoma (RCC) and non-small-cell lung cancer (NSCLC) (Routy et al., 2018). Studies in 2020 further linked gut microbiome diversity to improved ICI outcomes, with species such as *Akkermansia muciniphila* emerging as key indicators. Preclinical studies have also revealed the mechanisms by which the gut microbiome influences ICI efficacy, with specific bacterial strains enhancing immune responses, such as *Bifidobacterium pseudolongum*, which increased CD8+ T-cell activity via inosine production (Chen et al., 2021). Additionally, recent clinical studies in 2021 showed that FMT could overcome resistance to anti-PD-1 therapy in patients with melanoma, further emphasizing the therapeutic potential of manipulating the gut microbiome for cancer treatment (Baruch et al., 2021).

In one of the 2023 studies, it has been mentioned that the composition of the gut microbiota influences ICI response in both animal models and humans. They have shown that in mice, a beneficial response to PD-1 therapy was associated with an increase in *Bifidobacterium* species, and cohousing nonresponding mice with responders transferred the beneficial effect. Similarly, in humans with advanced hepatobiliary cancers, a higher abundance of *Lachnospiraceae* bacterium-GAM79 was linked to longer progression-free survival (PFS) and overall survival (OS), while *Veillonellaceae* species were associated with poorer outcomes (Abenavoli et al., 2023). In Zhou et al. study, it is mentioned that antibiotic use has also been shown

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to negatively impact ICI treatment outcomes, with studies indicating that antibiotics administered shortly before ICI therapy can result in worse OS, particularly in esophagogastric cancer patients (Ohm and Abdel-rahman 2023). However, this effect was reduced when the gap between antibiotic use and ICI treatment was extended.

In Bredon's study, it is highlighted the critical role of *Faecalibacterium prausnitzii*, particularly its EXL01 strain, in enhancing ICI therapy responses (Bredon et al., 2024). Moreover, clinical and preclinical data demonstrate that higher fecal levels of *F. prausnitzii* correlate with improved OS in patients receiving ICIs, particularly in the absence of antibiotic-induced microbiota perturbations. And Chang et al., investigated the gut microbiota and cytokine profiles of 74 cancer patients undergoing ICI therapy, categorizing them as benefiters or nonbenefiters based on PFS and OS (Chang et al., 2024). Benefiters had significantly longer PFS and OS than nonbenefiters. The gut microbiota of benefiters was more similar to healthy controls, characterized by higher levels of *Faecalibacterium prausnitzii*, *Fusicatenibacter saccharivorans*, and *Lachnospiraceae incertae sedis*, while nonbenefiters exhibited increased *Escherichia/Shigella* and reduced diversity.

Moreover, in Voigt et al.'s study, dysbiosis has been linked to resistance to immunotherapy, with certain gut microbiome signatures associated with better or worse responses to ICIs (Voigt et al., 2024). Beneficial microbiota, including *Bacteroidales, Verrucomicrobiaceae, Lachnospiraceae, Eubacterium,* and *Bifidobacterium,* are linked to improved responses, while bacteria from the Actinobacteria and Proteobacteria phyla, including *Escherichia coli* and *Klebsiella,* are associated with nonresponse. Notably, SCFA-producing bacteria, which are beneficial, have been shown to correlate with positive ICI outcomes. Clinical trials have explored interventions like adding live bacterial products, such as *Clostridium butyricum*, to ICI therapy, leading to improved PFS and OS rates (Ren et al., 2024). A study combining FMT with ICI therapy also showed favorable clinical responses, especially in patients with a specific donor microbiota.

Notably, FMT from ICI responders, combined with anti-PD-1 therapy, showed clinical benefits in patients with melanoma who were previously refractory to the treatment. FMT led to increased abundance of specific microbial taxa, such as *Ruminococcaceae* and *Bifidobacteriaceae*, which were associated with enhanced CD8+ T-cell activation and altered immune cell profiles. These findings, supported by proteomic and metabolomic analyses, suggest that the gut microbiome directly influences the immune response to ICIs (Davar et al., 2021). Clinical trials are now investigating the safety and efficacy of actively modulating the gut microbiome through various strategies, including probiotics, FMT, and microbial communities, to improve ICI therapy outcomes. These efforts may provide new ways to enhance cancer immunotherapy, particularly in tumors with low mutational burdens, such as prostate cancer, where ICI efficacy has been limited.

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MECHANISM OF INTERPLAY BETWEEN GUT MICROBIOME AND IMMUNE CHECKPOINT INHIBITORS

The gut microbiome influences the response to ICIs through several mechanisms. First, immune cell trafficking plays a significant role. Specific gut microbes can educate both innate and adaptive immune cells, which then travel to the TME to enhance antitumor immunity. These microbes produce chemotactic factors such as CXCL9 and CXCL10, which attract immune cells such as central memory CD4+ T cells expressing CCR9 or CXCR3 to the tumor sites (Jang et al.,2021). This process has been shown to increase the presence of tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, which are critical for immune responses against cancer (Lee et al., 2022).

Second, molecular mimicry may occur between gut microbial antigens and tumor neoantigens. T cells from patients treated with ICIs have been found to react to both gut microbes and tumor antigens, suggesting that gut microbial exposure can activate T cells to recognize tumor cells as well (Xinyu Liu et al., 2024). This cross-reactivity may enhance the immune response and contribute to improved clinical outcomes. For example, T cells stimulated with *Akkermansia muciniphila*, a microbe enriched in ICI responders, produced IFN-γ and were associated with prolonged PFS, indicating that microbial antigens might boost the antitumor immune response (Routy et al., 2018).

Finally, the microbiome can exert metabolic effects that influence immune responses. Certain gut microbes produce metabolites such as SCFAs and secondary bile acids, which have significant effects on the immune system. These metabolites can modulate immune activity not only within the gut but also at distant tumor sites, enhancing the efficacy of ICIs. For example, metabolites, such as anacardic acid and mevalonate, identified in ICI responders may influence the immune system and contribute to better antitumor responses (Frankel et al., 2017). This metabolic modulation provides another pathway through which the gut microbiome enhances the effectiveness of immunotherapy.

FUTURE PROSPECT: THERAPEUTIC STRATEGIES TARGETING THE GUT MICROBIOME IN TREATING CANCER

Therapeutic strategies targeting the gut microbiome are emerging as a promising approach to enhance cancer treatment, particularly immunotherapy, by modulating microbial composition to improve treatment efficacy and reduce adverse effects.

Fecal Microbiota Transplantation

Fecal microbiota transplantation represents one of the most direct approaches to modifying the gut microbiome. This process involves transferring fecal

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material from a donor to beneficiaries via oral administration of lyophilized capsules or through direct delivery methods such as colonoscopy or gastroscopy (Sarkar et al., 2023).

Recent studies have demonstrated that FMT may also play a role in enhancing antitumor immunity. A preclinical study involving fecal microbiota transfer from longer OS to shorter OS of pancreatic adenocarcinoma showed that FMT not only reconstituted the gut microbiome but also influenced tumor microbiome composition, tumor growth, and immune cell infiltration. These findings compel clinicians to find the association between favorable gut microbiota and cancer therapy (Xuliang Liu et al., 2024).

Moreover, clinical trials are underway to evaluate the potential of FMT in improving immunotherapy outcomes for patients with recurrent tumors or therapeutic resistance. Despite these promising findings, safety concerns regarding FMT persist. Since FMT is a relatively recent therapeutic approach, long-term safety data are limited, and adverse events have been reported. Minor side effects, such as abdominal cramps, bloating, and sore throat, have been observed in patients with ulcerative colitis or *C. difficile* infections receiving FMT. However, more serious complications, including bacterial infections, have also been documented. The FDA emphasized the importance of stringent donor screening to exclude those harboring potentially pathogenic bacteria. Other adverse events, such as aspiration during sedation for colonoscopy-administered FMT, have also been reported.

While adverse events associated with FMT have been noted, it is often challenging to determine whether they are directly linked to the procedure. For instance, vomiting, a common occurrence in various clinical settings, is also observed after FMT. To address these concerns, randomized controlled trials are needed to better assess and minimize potential risks.

Probiotics and Bacterial Consortia

Probiotics are live microorganisms or combinations of microorganisms that confer health benefits when consumed in appropriate amounts. Unlike untargeted FMT, probiotics aim to specifically modulate the gut microbiome, often by introducing beneficial microbial strains into the gut ecosystem. Over the time, probiotics are consumed in the form of supplements and functional foods. However, next-generation probiotics are being developed with a more targeted approach, incorporating single or multistrain bacterial communities based on robust scientific evidence of their efficacy. These next-generation probiotics serve in such a way that they not only restore function but also make the environment sustain the function.

In addition to changes in gut microbiota composition, researchers are examining how probiotics influence the TME (August, Verhaert, and Aspeslagh 2024). Probiotics have also been tested in combination with

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cancer immunotherapies such as ICIs. While probiotics have shown promise in enhancing cancer immunotherapy, certain bacteria have been identified as potentially detrimental. For example, *Blautia obeum* has been linked to a harmful immunophenotype and increases the risk of colitis due to ICI. Similarly, the effects of *Bacteroides* are mixed, as they may promote regulatory T-cell expansion or anti-inflammatory cytokine production, which can be either detrimental or favorable depending on the context.

Traditional probiotics have a well-established safety record in both daily and clinical use. However, next-generation probiotics, which are developed using advanced sequencing and analytical tools, present new challenges. Moderate overlaps in the bacterial taxa identified across studies highlight the need for standardized microbiome sequencing techniques and improved metabolomic profiling. Factors such as type of cancer, geography, host's diet, and environmental factors must also be considered to enhance the precision and efficacy of next-generation probiotics in cancer therapy.

Additionally, researchers are exploring whether immunotherapy resistance in certain patients is solely due to gut microbiome imbalances. Primary resistance may also stem from tumor-intrinsic oncogenic pathways and specific features of the TME.

Prebiotics

Prebiotics are fermentable and indigestible chemicals or substrates which enhance the growth of specific microorganisms, fostering a diverse and healthy microbiota. Unlike probiotics, prebiotics have a selective advantage to beneficial microbes. Since prebiotics are composed primarily of carbohydrates, prebiotics pass undigested into the large intestine, where they undergo fermentation by commensal bacteria, producing SCFAs. For instance, *Faecalibacterium prausnitzii*, *A. muciniphila*, *Bifidobacterium* spp., *Lactobacillus* spp., and *Streptococcus* spp. are SCFA-producing bacteria which found in increased abundance in responder groups of clinical trials (Botticelli et al., 2020), (Jin et al., 2019), being positively correlated with anti-PD-1/PD-L1 treatment responses in patients with lung (Grenda et al., 2022), gastrointestinal (Peng et al., 2020), and hepatocellular cancer (Zheng et al., 2019), or melanoma (Matson et al., 2018). Moreover, this fermentation lowers intestinal pH which supports the growth of beneficial microbes.

However, resistant starch is one of the most extensively researched prebiotics which facilitates the growth of bacteria which are involved in butyrate production. Research indicates that prebiotics enhance the therapeutic efficacy of chemotherapy and radiotherapy while reducing their toxicity (Li et al., 2019).

Emerging evidence also highlights the role of microbial metabolites, such as inosine, in modulating immunotherapy responses. A study identified inosine which is produced by *Bifidobacterium pseudolongum*, as a metabolite

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that promotes antitumor responses to ICIs in germ-free mice with various tumor types, including melanoma, bladder, and colorectal cancer (Samami et al., 2024). However, the efficacy of inosine relies on adenosine A2A receptor expression and requires T-cell costimulation which demonstrates its potential in enhancing immunotherapy outcomes (Ni et al., 2023).

Dietary and Lifestyle

The interplay between diet, lifestyle, and the gut microbiota has been a focus of research due to its profound impact on health and disease, including cancer. Gut microorganisms play a crucial role in food digestion and nutrient extraction, influencing microbial communities in the gastrointestinal tract. These microorganisms release substances that alter the nutritional availability of food, and dietary changes whether short- or long-term can significantly influence microbial transcriptomic and metabolomic profiles. For instance, high-fat diets have been linked to a reduction in beneficial bacteria such as *Bifidobacterium* spp. and *Bacteroides*, while increasing proinflammatory microbes through the formation of taurine-conjugated bile acids. Conversely, plant-based diets have been shown to increase fiber-degrading bacterial taxa, enhancing SCFA production. However, reduced carbohydrate and fiber intake dramatically decreases these beneficial bacteria, as observed in a human cohort study (Chen et al., 2021).

Moreover, lifestyle factors also shape the gut microbiome and influence cancer outcomes. For example, alcohol consumption increases the risk of colorectal cancer in a dose-dependent manner, while the refrainment from alcohol can restore gut barrier integrity. However, Chronic ethanol exposure reduces the abundance of butyrate-producing bacteria, such as *Faecalibacterium prausnitzii* and *Coprococcus eutactus*. Interventions targeting lifestyle and behavior, such as integrative oncology programs, aim to improve cancer-related outcomes through diet, exercise, and the management of the environment. Furthermore, observational studies have been designed to explore the impact of microbiomes on cancer therapy efficacy (Shaikh, Gills, and Sears 2019).

CHALLENGES IN IMPLEMENTING GUT MICROBIOTA IN THERAPEUTIC STRATEGIES

Although the gut microbiome holds great promise in enhancing cancer therapies, especially immunotherapy, still there are challenges that need to be addressed. For instance, the presence of unfavorable gut bacteria can reduce treatment efficacy, while antibiotics may cause dysbiosis due to their nonspecific nature. Prebiotics and their combination with specific beneficial bacteria show promise by promoting the growth of bacteria that support antitumor immunity, while bacteriophages offer targeted removal of harmful bacteria. FMT also shows potential but requires careful donor

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selection to ensure a diverse and beneficial microbial composition and to minimize pathogen transfer risks (Frankel et al., 2017). Alternatively, specific beneficial bacteria can be isolated, cultured, and encapsulated to maintain their therapeutic efficacy. Current sequencing methods may overlook less abundant but functionally critical microbes, emphasizing the need for research on rare species. Variability in findings across studies—driven by differences in patient genetics, environments, tumor types, and experimental models—highlights the complexity of gut microbiome interactions. For instance, while some studies report that *Bacteroides fragilis* impairs immunotherapy response, others suggest its beneficial role, and the effects of antibiotics on treatment outcomes remain inconsistent. Mouse models also have limitations in replicating human TMEs, complicating translational research. The immune system's influence on the gut microbiota, as well as the impact of lifestyle factors such as diet, sleep, and exercise, further underscores the need for personalized approaches. Standardized methodologies, a deeper understanding of immune-microbiota interactions, and exploration of microbial profiles across diverse patient cohorts are critical to improving gut microbiome-based cancer treatments.

Moreover, immune-related adverse events (irAEs) are a significant concern in immunotherapy, particularly with ICIs. The risk of irAEs is higher in patients receiving anti-CTLA-4 therapy compared to those on anti-PD-1 and anti-PD-L1, and the incidence increases when both therapies are combined (Zoghbi et al., 2024). The gut microbiome has been linked to the development of these toxicities. Studies have shown that the abundance of certain microbiota, particularly species within the Bacteroidetes phylum, is associated with resistance to colitis in patients treated with anti-CTLA-4 (Hirata et al., 2024). In contrast, patients who developed colitis exhibited a shift in their gut microbiota, marked by decreased microbial diversity and a reduction in Firmicutes species, particularly *Ruminococcus*, Lachnospiraceae, and *Clostridium* IV, while Bacteroidetes levels remained higher in those who did not develop colitis. These findings suggest that the composition of the gut microbiome plays a role in modulating the risk of irAEs during immunotherapy.

CONCLUSION

The association between the gut microbiome and ICIs has revealed the critical role of the gut microbiome in shaping the efficacy and toxicity of these therapies. Clinical and preclinical studies consistently demonstrate that specific gut microbial compositions and functions are associated with enhanced ICI responses, primarily through modulation of immune cell activation, cytokine profiles, and TME dynamics. Moreover, dysbiosis and antibiotic-induced disruptions of the gut microbiome have been linked to reduced therapeutic efficacy and increased irAEs.

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Microbiome profiling has emerged as a valuable tool to identify potential biomarkers for predicting ICI outcomes (Pavelescu et al., 2024). High microbial diversity and the presence of specific bacterial taxa, such as *Akkermansia muciniphila*, *Bifidobacterium longum*, and *Faecalibacterium prausnitzii*, are associated with better response to cancer therapy. Integrative metagenomics and metabolomics approaches further aid in identifying microbial metabolites, such as inosine and anacardic acid, that correlate with improved immune responses (Samami et al., 2024).

Microbiome modulation strategies, including FMT, probiotics, synbiotics, and dietary interventions, have shown promise in preclinical and early-phase clinical studies to enhance ICI efficacy. FMT from responders, in particular, has demonstrated the ability to reverse resistance to ICIs and improve patient outcomes. However, standardized protocols, rigorous safety assessments, and understanding the long-term effects of these interventions remain critical.

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