

Gut Microbiota–Tumor Microenvironment Interactions: Mechanisms and Clinical Implications for Immune Checkpoint Inhibitor Efficacy in Cancer

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Abstract: Cancer immunotherapy has transformed cancer treatment in recent years, with immune checkpoint inhibitors (ICIs) emerging as a key therapeutic approach. ICIs work by inhibiting the mechanisms that allow tumors to evade immune detection. Although ICIs have shown promising results, especially in solid tumors, patient responses vary widely due to multiple intrinsic and extrinsic factors within the tumor microenvironment. Emerging evidence suggests that the gut microbiota plays a pivotal role in modulating immune responses at the tumor site and may even influence treatment outcomes in cancer patients receiving ICIs. This review explores the complex interactions between the gut microbiota and the tumor microenvironment, examining how these interactions could impact the effectiveness of ICI therapy. Furthermore, we discuss how dysbiosis, an imbalance in gut microbiota composition, may contribute to resistance to ICIs, and highlight microbiota-targeted strategies to potentially overcome this challenge. Additionally, we review recent studies investigating the diagnostic potential of microbiota profiles in cancer patients, considering how microbial markers might aid in early detection and stratification of patient responses to ICIs. By integrating insights from recent preclinical and clinical studies, we aim to shed light on the potential of microbiome modulation as an adjunct to cancer immunotherapy and as a diagnostic tool, paving the way for personalized therapeutic approaches that optimize patient outcomes.

Keywords: ICIs, immunotherapy, gut microbiota, microbiome, tumor microenvironment

Introduction

The growing resistance of cancer to traditional therapies has led scientists to explore new treatment approaches. In recent decades, immunotherapy has emerged as a groundbreaking method, with several drugs showing significant success, particularly when combined with other therapies. Notably, patients with advanced metastatic non-small cell lung cancer (NSCLC) treated with immune checkpoint inhibitors (ICIs) have shown markedly improved survival outcomes compared to those receiving chemotherapy.¹ Despite these advancements, immunotherapy still faces challenges in terms of efficacy for certain cancers.

A promising avenue for enhancing immunotherapy involves the human microbiome. Emerging evidence suggests that incorporating the microbiome can boost the effectiveness of immunotherapy and improve cancer outcomes.² As a result, research has focused on understanding the impact of the gut microbiome on human health and its potential to optimize cancer therapies. Recent studies have identified associations between specific gut microbiota and treatment success, particularly with ICIs targeting PD-1, PD-L1, and CTLA-4.³ The gut microbiome plays a critical role in modulating the immune system, including its response to cancer therapies. It enhances immune function through mechanisms such as releasing short-chain fatty acids, interacting with toll-like receptors, and producing IgA to prevent bacterial invasion.⁴ These effects have spurred interest in reprogramming gut microbiota to improve immune responses across various contexts.

While the microbiome is being leveraged to enhance cancer therapies, changes in microbiome composition during prolonged treatment have been observed. The relationship between the gut microbiome, immune system, and cancer is complex, requiring a better understanding of how these interactions affect drug resistance and treatment outcomes.

A deeper understanding of these mechanisms could transform cancer treatment strategies. This review summarizes the latest findings on the role of microbiota in modulating immune checkpoint inhibitors in cancer treatment.

Gut Microbiota: Structure, Diversity, and Health

The human body hosts trillions of microbiomes, including bacteria, fungi, viruses, and archaea, residing in or on various surfaces. Colonization of gut microbiomes begins early in life, with the mode of delivery influencing an infant's gut microbiome diversity. Infants born via caesarian section tend to harbor more opportunistic microbes, such as *Staphylococcus*, *Haemophilus*, *Enterobacter cancerogenus*, *Hormaechei*, and *Veillonella* species, compared to those delivered vaginally.⁵ The adult gut contains between 10^{13} and 10^{14} microbiomes, comprising over 1000 microbial species and more than 7000 bacterial strains.⁴ Gut microbiome composition varies based on factors like age, race, sex, geography, and lifestyle, including diet, prebiotics, and probiotics. Among these, bacteria are the most common commensal organisms, primarily colonizing the gastrointestinal tract, where their metabolites regulate physiological processes like mental health, inflammation, and immunity.

Imbalance in the microbiome (dysbiosis) is linked to diseases such as diabetes, asthma, allergies, autism, cardiovascular, neurological, and cancer-related conditions.⁶ Dysbiosis reflects changes in microbial diversity and abundance. Early microbiome research relied on culturing techniques, but many microbes are unculturable. Modern approaches such as 16S rRNA sequencing, metagenomics, transcriptomics, and proteomics have allowed researchers to differentiate between healthy and diseased microbiomes.⁷

16S rRNA sequences are mapped and clustered into operational taxonomic units (OTUs) based on sequence similarities. Next-generation sequencing offers diversity indices that mathematically describe the complexity of microbiome samples and their differences. In 1960, Whittaker introduced the concept of “gamma diversity” (total species diversity within a landscape), which comprises “alpha diversity” (within-sample diversity) and “beta diversity” (differences between samples).⁸ High alpha diversity indicates a sample with numerous abundant species, while low beta diversity suggests that two samples share most species.

Early classifications of healthy microbiomes were based on their resilience to stress and ability to recover from disturbances.⁶ Recent research has highlighted the role of dysbiotic microbiota in cancer therapy and cardiotoxicity.⁹ In 2017, the interaction between microbiota and cancer treatments gained attention, particularly in the context of immunotherapy. Routy et al demonstrated that lung and kidney cancer patients with primary resistance to PD-1 inhibitors had lower levels of *Akkermansia muciniphila*, a mucus-degrading bacterium, compared to responders.¹⁰ Restoring immune responses through fecal transplants or oral supplementation of *Akkermansia muciniphila* has shown promise in mouse models of epithelial tumors.¹¹ Additionally, studies in melanoma patients have revealed a healthier microbiota profile in responders to PD-1 inhibitors compared to non-responders.

Gut Microbiota-Immune System Crosstalk

Gut microbiota play a crucial role in digestion by producing metabolites that nourish gastrointestinal (GI) epithelial cells and protect against pathogens. The immune system in the intestine acts as a protective barrier, preventing gut microbes from crossing the epithelial layer while avoiding inappropriate immune responses to commensal bacteria in the intestinal lumen. This balance helps reduce the risk of diseases like inflammatory bowel disease and celiac disease, as well as other immune-related disorders. The gut immune system maintains a delicate equilibrium between pro-inflammatory and anti-inflammatory responses, and this regulation is essential for immune homeostasis in conditions such as obesity, cancer, and Parkinson's disease.⁵ The interaction between gut microbiota and the host's immune system is a complex and dynamic process that either maintains physiological stability or contributes to disease development. The immune system consists of two main components: the innate and adaptive systems, which work together to neutralize immunological threats without triggering excessive immune responses. However, in certain chronic diseases and inflammatory conditions, the immune system may become overactive, leading to adverse outcomes and complicating treatment.

Initially, innate immune cells—such as dendritic cells, natural killer cells, macrophages, and polymorphonuclear cells—provide the first line of defense against pathogens. These cells release chemokines and cytokines, signaling adaptive immune cells like B cells, T cells, and regulatory T cells to join in eliminating the invading agent.

Neonatal Gut Microbiota Shapes the Immune System

Gut microbiota begin to form during delivery or shortly after birth, with the composition depending on the method of delivery. In vaginal births, a newborn's microbiota closely resembles the mother's vaginal and fecal microbiota, while cesarean section deliveries result in microbiota acquired from the immediate environment and skin. Newborns also receive secretory immunoglobulin A (SIgA) from their mother, which is critical for developing both their immune system and microbiota.¹² SIgA neutralizes toxins, binds to M cells in the gut epithelium, and coats non-invasive pathogens, facilitating the activation of B and T cells. The proximal small intestine has the highest concentration of SIgA-coated microbiota, followed by the distal small intestine and colon. This process helps the immune system recognize and eliminate harmful pathogens, promoting overall health.

During intrauterine development, maternal FOXP3⁺ CD4⁺ regulatory T cells suppress the fetal innate immune response to maternal antigens. However, delays in microbiota colonization and low microbial diversity in newborns can affect the maturation of adaptive immune cells. A Swedish study on 65 children found that early gut colonization significantly influenced T cell development. The presence of *Bifidobacterium* in the neonatal gut during the first week of life was linked to increased production of cytokines like IL-5, IL-6, IL-13, TNF, and memory CD45RO⁺CD4⁺ T cells by 36 months.¹³ By age three, gut microbiota such as *Enterococcus*, *Staphylococcus aureus*, and *Clostridium* were associated with IL-13, IL-5, and TNF production. Additionally, at 4 and 8 months, the presence of CD27⁺ memory B cells was linked to both *Bifidobacterium* and *E. coli*.¹³ The composition of infant gut microbiota has changed over time. Previously, it was dominated by *Clostridium difficile* with low diversity, but recent studies show an increased presence of *E. coli*, *Bacteroides*, coagulase-negative *Staphylococcus*, and *S. aureus* in the infant gut lumen.

Gut Microbiota-Innate Immune System Axis

The intestinal epithelium, consisting of multiple structural layers, works with gut microbiota as the first line of defense against pathogens and inflammatory disorders. This barrier is composed of a pre-epithelial mucus layer, the epithelial layer (including M cells, Paneth cells, epithelial cells, and mucipare cells), and a post-epithelial layer with immune cells like dendritic cells, lymphocytes, and macrophages.¹⁴ The mucus layer contains tight junction proteins and antimicrobial peptides (AMPs), which help protect against bacterial invasion. Paneth cells, predominantly located in the small intestine, are essential for host-microbiota interactions. These specialized epithelial cells express receptors like Toll-like receptors (TLRs), RIG-I-like receptors, and NOD-like receptors, which recognize bacterial patterns and activate protective responses.^{14,15} Paneth cells also produce antimicrobial peptides, such as defensins, that not only defend against pathogens but also help shape the composition of the microbiota.^{14,16}

The gut's innate immune defense involves a variety of strategies to maintain homeostasis. The mucus layer, AMPs, and secretory IgA (SIgA) play key roles in keeping commensal microorganisms balanced while ensuring a protective immune response. Intestinal epithelial cells (IECs) also regulate immune responses through the MyD88 and NF- κ B pathways in response to commensals, while TLR-2 signaling maintains epithelial integrity¹⁶ (Figure 1C). IECs secrete signals that regulate innate lymphoid cells (ILCs), which in turn produce cytokines associated with different immune responses (Th1, Th2, and Th17) (Figure 1B). Despite lacking antigen recognition, ILCs release a range of cytokines, such as IFN- γ , IL-5, IL-13, IL-17A, and IL-22, which help maintain gut immune homeostasis.

In response to commensal microbe signals, IECs secrete immunoregulatory molecules like TGF- β , thymic stromal lymphopoietin (TSLP), and retinoic acids. These signals activate dendritic cells (DCs) and macrophages, which promote a tolerogenic immune environment by producing IL-10 and retinoic acids.⁵ CD103⁺ DCs, a dominant subset of intestinal macrophages, present antigens to T cells in secondary lymphoid organs, like Peyer's patches and mesenteric lymph nodes. Activated T cells secrete TGF- β , promoting the development of regulatory T cells that help prevent excessive inflammation. Additionally, intestinal macrophages remove pathogens and commensal bacteria that penetrate the epithelial barrier.¹⁶

When invasive pathogens or pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides cross the epithelial barrier, they trigger goblet cells to release mucin and reinforce the mucus layer. PAMPs are recognized by TLRs on innate immune cells like neutrophils, DCs, and macrophages, initiating an immune response.^{5,14} Gut microbiota also influence gut-associated lymphoid tissue (GALT), stimulating innate immune cells, such as DCs and natural killer

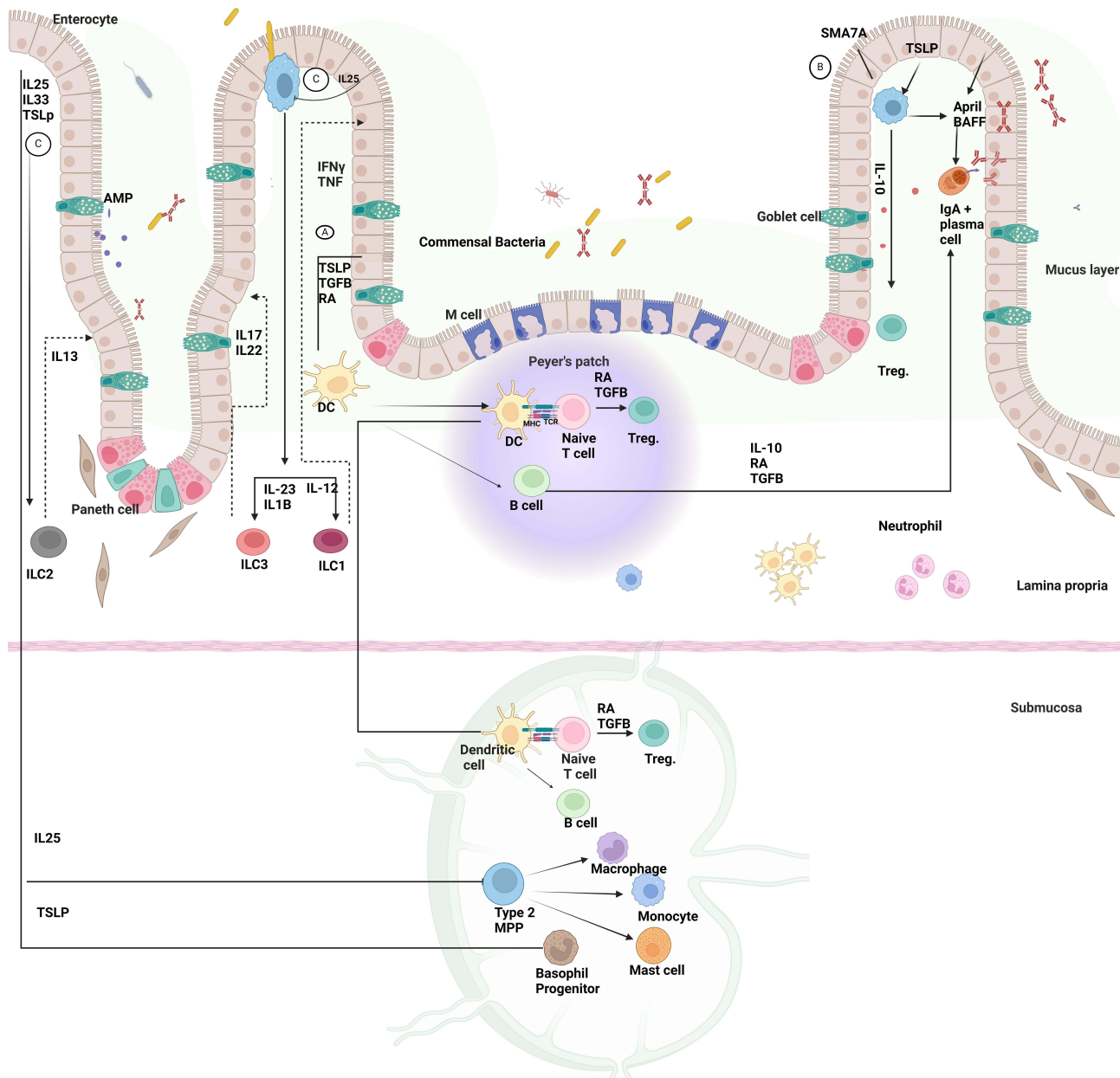


Figure 1 The interaction between commensal bacteria and intestinal epithelial cells influences the innate and adaptive immune systems' ability to maintain homeostasis and prevent inflammation. In response to microbiota signals, IECs interact with their immediate environment, identify microbial signals, and mediate the gut immune response in a regulatory process. **(A)** Tolerogenic function is achieved through the production of thymic stromal lymphopoietin (TSLP), TGF-beta, and RA by stimulating DCs. Activated DCs then travel to Mesenteric lymph nodes and Peyer's patch, where they interact with naïve T cells, leading to Treg development and differentiation of naïve B cells into Ig A+ secreting plasma cells. **(B)** Furthermore, the regulatory function of IECs that produce semaphorin 7A SEMA7A has been established by activating IL10-producing macrophages and T regs. **(C)** IECs secreted cytokines, such as thymic stromal lymphopoietin (TSLP), which causes basophil progenitor cells to differentiate into basophils, and interleukin-25 (IL-25), which promotes the formation of monocytes, mast cells, basophils, and macrophages from type 2 multipotent progenitor cells. Moreover, IEC-derived cytokines govern the development of innate lymphoid cells into three groups: ILC1, ILC2, and ILC3. Created in BioRender. Nabeel, W. (2025) <https://BioRender.com/h28g657>.

cells, in response to pathogens. Certain bacteria, including *Lactobacilli* and *Clostridium*, help regulate the inflammatory response by promoting regulatory T cell activity.¹⁴ Normally, the innate immune system efficiently clears pathogens, but if compromised, pathogens can spread to systemic circulation, potentially leading to sepsis.

Several factors, such as antibiotics, NSAIDs, and aging, can disrupt the balance of gut microbiota, leading to the overgrowth of pathogenic organisms like *Clostridium difficile*, which can cause infection and diarrhea. *C. difficile* toxins activate innate immune cells via TLR4, TLR5, and NOD1, triggering the release of pro-inflammatory cytokines like IL-12, IL-18, and IFN-γ, which contribute to infection severity.¹⁷ Recent studies have shown that *Bifidobacterium longum*

BB536 can enhance innate immunity by increasing the expression of activation markers (CD86 and HLA-DR) on dendritic cells and promoting the release of pro-inflammatory cytokines like IFN- α 1 and IFN- β .¹⁸

Gut Microbiota-Adaptive Immune System Axis

Bacterial invasion of the epithelial layers and subsequent entry into mesenteric lymph nodes (MLNs) or systemic circulation triggers the adaptive immune system, which consists of humoral and cellular components. Antigen-presenting cells (APCs), such as dendritic cells, macrophages, and neutrophils, present bacterial antigens to T lymphocytes, particularly intraepithelial lymphocytes (IELs) and lamina propria lymphocytes. Notably, intraepithelial $\gamma\delta$ T cells play a vital role in the adaptive immune response by secreting cytokines and antimicrobial compounds, serving as a defense mechanism against numerous infections. These $\gamma\delta$ T cells, found in mucosal barriers like the lungs, skin, and gut, are crucial for maintaining immune balance.^{19,20}

Invasive pathogens in the bloodstream correlate with a reduction in $\gamma\delta$ T lymphocytes within epithelial layers, increasing vulnerability to infections. Studies show that the loss or insufficiency of mucosal T lymphocytes adversely impacts outcomes in enteric infections. Additionally, some gut microbiota and their metabolites stimulate $\gamma\delta$ T cells. Antibiotic use can disrupt gut microbiota, causing hypoxia in the intestinal tract and altering its composition. This shift often results in a decrease in *Clostridium* and an increase in *Desulfovibrio*, leading to the activation of $\gamma\delta$ T cells.²⁰ $\gamma\delta$ T cells exhibit dual roles as both innate and adaptive immune cells. In conditions such as inflammatory bowel disease (IBD), these cells release pro-inflammatory cytokines like IL-17A, TNF- α , and IFN- γ , contributing to the disease's pathology.²⁰

Commensal microbiota plays a significant role in T cell activation. Microbial antigens stimulate dendritic cells (DCs) to release IL-6 via TLR/MyD88-dependent and independent pathways, activating T cells.²¹ MyD88 serves as a key adaptor for innate immune receptors recognizing microbial signals. Its deficiency impacts microbiome composition, as shown in studies linking MyD88 signaling to the prevention of type 1 diabetes by modifying gut microbiota.^{22,23}

Moreover, specific subtypes of T cells are activated by certain bacteria more than others, with segmented filamentous bacteria (SFB) identified as major inducers of intestinal Th17 cells. Innate IL-23 production can modify Th17 responses within the gut, further emphasizing the complex relationship between microbiota and the immune system.²¹

Additionally, polysaccharides from *Bacteroides fragilis* activate IL-10-producing Foxp3⁺ regulatory T cells through the TLR2 pathway.

Recent research has also explored $\gamma\delta$ T cells' role in immune responses against lung cancer and their interactions with microbiota. Lung cancer progression has been linked to the activation of $\gamma\delta$ T cells and certain microbiota. Inhibiting $\gamma\delta$ T cells, microbiota, or their metabolites can hinder lung cancer development.¹⁹ Lung microbiota, such as *Propionibacterium acnes*, *Aneurinibacillus aneurinilyticus*, and others, contribute to lung cancer by stimulating neutrophils and alveolar macrophages to release IL-1B and IL-23, which in turn activate $\gamma\delta$ T cells and promote inflammation.¹⁹ T cell activation is also influenced by microbial composition. For example, the activation of CD8⁺ cytotoxic T cells is initiated by APCs recognizing microbial antigens, with cytokines from CD4⁺ T cells further stimulating cytotoxic responses. This underscores the importance of understanding the interplay between gut microbiota and systemic immunity.¹⁷

Follicular helper T (Tfh) cells, which play a crucial role in regulating microbiota composition, also interact with gut microbes. Research has found that Tfh differentiation is influenced by microbiota, with specific deficiencies, such as in PD-1 or P2RX7, linked to altered microbiota composition.²⁴ SFB has been shown to promote Tfh differentiation in Peyer's patches, influencing effector CD4⁺ T helper cell responses by limiting IL-2 access. Tfh cells are essential for supporting B cell functions, such as memory B cell development, affinity maturation, and germinal center formation.

In conclusion, the interaction between microbiota and T lymphocytes shapes both the innate and adaptive immune systems. This complex relationship highlights the profound impact that gut microbiota can have on overall immune function and health. Figure 1 demonstrated the interactions of gut microbiota with the innate and adaptive immune systems.

Dysbiosis Associated Cancer

Initial research aimed to identify strains of healthy microbiota such as *Prevotella copri*, *Ruminococcus obeum*, *Bacteroides finegoldii*, and *Lachnobacterium bovis*.⁶ The microbiome's composition in different body sites can reflect transitions from healthy to diseased states and the transmission of microbiota between these sites. Dysbiosis of gut

microbiota can lead to pathological issues and trigger immune responses to disease treatments. Colorectal cancer (CRC), the third most common cancer globally, has garnered significant attention, with an expected incidence of 2.2 million cases by 2030.^{25,26}

Studies have shown that patients with CRC who develop metastasis often present with altered intestinal microbiota, including strains like *Fusobacterium*, *Selenomonas*, *Prevotella*, and *Bacteroides*.²⁷ The gut microbiota in CRC patients differs significantly from that of healthy individuals, and various factors beyond microbiota—including inflammation, bacterial metabolites, virulence factors, and genotoxicity—may influence CRC treatments.²⁶ While CRC results from multiple factors, including genetic and environmental influences, the microbiota is increasingly recognized as an environmental contributor to cancer development. Limited data exist on the relationship between microbiota and aging, but a study in rats found that while gut microbiota diversity decreases with age, *Firmicutes* increase and *Bacteroides* decline. *Ruminococcus* was shown to negatively correlate with pro-inflammatory cytokine IFN- γ levels, indicating a positive role in gut health.²⁸ Microbiome diversity correlates with tumor stage, suggesting potential microbial markers for cancer progression. For example, *Fusobacterium* and *Parvimonas* are more abundant in grade 3 CRC tumors, while *Fusicatenibacter*, *Blautia*, *Intestinomonas*, and *Romboutsia* are enriched in grade 2 tumors.²⁹ Metagenomic sequencing of fecal samples has revealed differences in microbiota diversity between young and old CRC patients. Younger patients had a greater diversity of bacteria, with species like *Flavonifractor plautii*, *Fusobacterium*, and *Odoribacter* more prominent, while older patients had less diversity, dominated by *Streptococcus*, *Fusobacterium*, and *Gemella*.²⁵ Tumor location and stage also affect microbiota composition. In older patients, *Fusobacterium* was more prevalent in early-stage (stage 0-III) CRC tumors on the left side, while *Christensenellaceae* was abundant in late-stage (stage IV) tumors on the right side.

Functional and metabolic analyses of microbiota are crucial in understanding CRC prognosis. The Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) analyses have highlighted distinct bacterial metabolites in young and old CRC patients. KEGG analysis showed higher short-chain fatty acid production in controls compared to CRC patients, while GO analysis found higher DNA and RNA binding activity in younger CRC patients, suggesting increased cellular invasion and proliferation.²⁵

Extracellular vesicles (EVs) derived from gut microbiota have been proposed as potential biomarkers for CRC diagnosis. A study involving 116 control patients and 91 CRC patients analyzed EVs from urine samples, finding significant differences between the two groups. CRC patients showed elevated levels of *Proteobacteria*, *Actinobacteria*, and *Firmicutes*, while *Bacteroides* and *Verrucomicrobia* were reduced compared to the control group. *Staphylococcus* and *Acinetobacter* were more enriched at the genus level in CRC patients.³⁰ Further analysis revealed no significant differences in alpha or beta diversity based on CRC location (proximal/distal) or between early and late-stage CRC groups.³⁰

In hepatocellular carcinoma (HCC), early-stage patients showed an abundance of *Acinetobacter*, while butyrate-producing bacteria and liposaccharide-producing bacteria were elevated compared to cirrhosis patients.³¹ Similarly, *Sellimonas* abundance is associated with a higher risk of estrogen receptor-positive breast cancer, while *Alphaproteobacteria* abundance correlates with a lower risk of prostate cancer.³²

Pancreatic cancer is associated with reduced microbiota diversity and a high prevalence of *Proteobacteria*. Studies have shown that the pancreatic microbiota differs significantly from that of the stomach and duodenum. In pancreatic ductal adenocarcinoma (PDAC), distinct bacterial compositions within the tumor microenvironment (TME) have been found to reduce anti-tumor immunity and promote tumor progression. The predominant microbiota in non-tumorous pancreatic tissue consists of *Proteobacteria* and *Firmicutes*. In PDAC, *Lactobacillus*, *Bacteroides*, and *Peptoniphilus* were significantly elevated, leading to reduced effector T cells and unfavorable immune responses. Some bacterial metabolites, like tryptophan produced by *Lactobacillus*, may exert immunosuppressive effects by inhibiting intertumoral macrophages.^{33,34}

Microbiome-Based Diagnostic Applications in Cancer

The gut microbiome, particularly through analysis of fecal and plasma samples, is emerging as a promising noninvasive tool for cancer diagnosis. Fecal microbiome analysis has been extensively explored for colorectal cancer (CRC) detection, with studies identifying specific bacterial markers linked to CRC. For instance, a gene marker from *Lachnoclostridium spp.* demonstrated a sensitivity of 48% and specificity of 79% for detecting



colorectal adenomas.³⁵ When combined with other bacterial species such as *Fusobacterium nucleatum*, *Clostridium hathewayi*, and *Bacteroides clarus*, sensitivity and specificity for CRC detection improved to 94% and 81%, respectively.³⁶ Similarly, *Clostridium symbiosum* showed promise as a CRC biomarker, yielding a sensitivity of 80% and specificity of 55%, outperforming the well-known cancer marker *F. nucleatum*.³⁷ This model achieved AUROC scores of 0.74 for early-stage CRC and 0.76 across all stages—higher than traditional fecal immunochemical tests (FIT). Notably, combining *C. symbiosum* with FIT further increased AUROC scores to 0.80 and 0.87, suggesting that fecal microbial markers can complement existing diagnostic methods.

Meta-analyses of fecal metagenomes across diverse CRC populations have also highlighted a core set of 29 enriched bacterial species, including *F. nucleatum* and *Parvimonas micra*, consistently differentiating CRC patients from controls with AUROC scores ranging from 0.71 to 0.92.^{38,39} Additional findings indicated elevated trimethylamine synthesis, potentially from *Lachnospiraceae* species and *H. hathewayi*, pointing to microbial pathway markers.⁴⁰ While these fecal microbiome signatures are robust across populations, it remains unclear whether they play a causative role in CRC or reflect downstream effects.

Microbial markers in the fecal microbiome have been studied in other cancers as well. A 16S rRNA analysis in lung cancer patients revealed significant shifts in 24 bacterial genera. A model based on nine of these genera, including *Bacteroides* and *Clostridium*, predicted lung cancer with an AUROC score of 0.76.⁴¹ These preliminary results highlight the potential of gut microbiota as diagnostic markers beyond CRC, although further validation across larger populations is required.

In addition to the gut microbiome, plasma cell-free DNA (cfDNA) is gaining interest as a diagnostic tool for cancer. Originally developed for prenatal testing, cfDNA assays—such as the FDA-approved cobas EGFR Mutation Test and Guardant360 CDx—now aid in cancer diagnostics, particularly for detecting mutations in non-small cell lung cancer (NSCLC).^{42,43} FoundationOne Liquid CDx, approved in 2020, expands this approach by screening over 300 genes associated with multiple cancers, including NSCLC, prostate, ovarian, and breast cancer.⁴⁴

More recently, researchers have investigated microbial DNA signatures in plasma cfDNA as potential cancer biomarkers. Next-generation sequencing of plasma from breast cancer patients, for example, revealed distinct microbial reads, with *Acinetobacter* spp. prevalent in controls and *Pseudomonas* spp. and *Sphingomonas* spp. in patients.⁴⁵ A diagnostic model trained on these microbial signatures successfully distinguished among 20 different cancer types and healthy controls, achieving AUROC scores consistently above 0.85. This accuracy was maintained for early-stage cancers (stages I and II), with AUROC scores exceeding 0.80. Fungal DNA signatures in plasma also demonstrated diagnostic potential, with combined bacterial and fungal data achieving an AUROC score of 0.92. These findings underscore the potential of plasma-based microbial cfDNA assays as an early-stage diagnostic tool, although further research is necessary to refine and validate these approaches.

Although these diagnostics show potential for detecting cancer experimentally, these methods are likely to complement, rather than replace, conventional techniques such as imaging and tissue biopsies in the near term. As our understanding of the microbiome's complex interactions with cancer progresses, however, such diagnostics could evolve into standalone approaches, particularly valuable for early detection and reducing the need for invasive procedures.

Effects of Gut Dysbiosis on Cancer Progression

Introduction to Gut Microbiota and Dysbiosis

The human gut microbiota is a complex ecosystem comprising diverse microorganisms, including bacteria, fungi, archaea, and viruses, predominantly made up of bacterial groups like Firmicutes and Bacteroidetes. This microbiota is integral in regulating metabolism, immune function, and maintaining overall balance in the intestinal tract.⁴⁶ The gut microbiota interacts closely with the host's mucosal immune system to promote tolerance to beneficial microbes and control harmful pathogens through mechanisms such as producing inhibitory metabolites, modulating immune responses, maintaining a protective mucus barrier, and competitively using nutrients.⁴⁷ This equilibrium is crucial for preventing pathological infections and ensuring overall health.

However, an imbalance in this microbial community, known as gut dysbiosis, has been linked to the pathogenesis and progression of various diseases, including cancer.⁴⁸ Dysbiosis disrupts fundamental processes within the host, contributing to cancer development through alterations in metabolic pathways, chronic inflammation, and compromised intestinal barrier function. For example, dysbiosis can lead to the production of carcinogenic compounds and reduce protective metabolites like short-chain fatty acids (SCFAs), which are known for their anti-inflammatory and anti-cancer properties.⁴⁹ Furthermore, dysbiosis can trigger chronic inflammation, a known cancer risk factor, and compromise the intestinal barrier, allowing toxic substances to enter the bloodstream and promote cancer progression.⁵⁰ Additionally, dysbiosis can weaken immune surveillance against tumors, as seen in colorectal cancer, where specific pathogenic bacteria such as *Fusobacterium nucleatum* create a pro-tumorigenic environment.⁵¹ Emerging research also indicates a potential link between dysbiosis and breast cancer through modulation of hormone-driven pathways.⁵² The intricate mechanisms by which gut dysbiosis influences cancer progression intersect with multiple hallmarks of cancer across various types as shown in Figure 2.

Sustaining Proliferative Signaling and Evading Growth Suppressors

In normal physiology, cellular growth signals are tightly regulated. Cancer cells, however, often acquire the ability to sustain these signals autonomously, bypassing typical regulatory mechanisms.⁵³ Gut dysbiosis can exacerbate this by altering the production of microbial metabolites that interact with signaling pathways. For instance, bacterial enzymes can convert primary bile acids into secondary bile acids, which act as signaling molecules that promote proliferation in

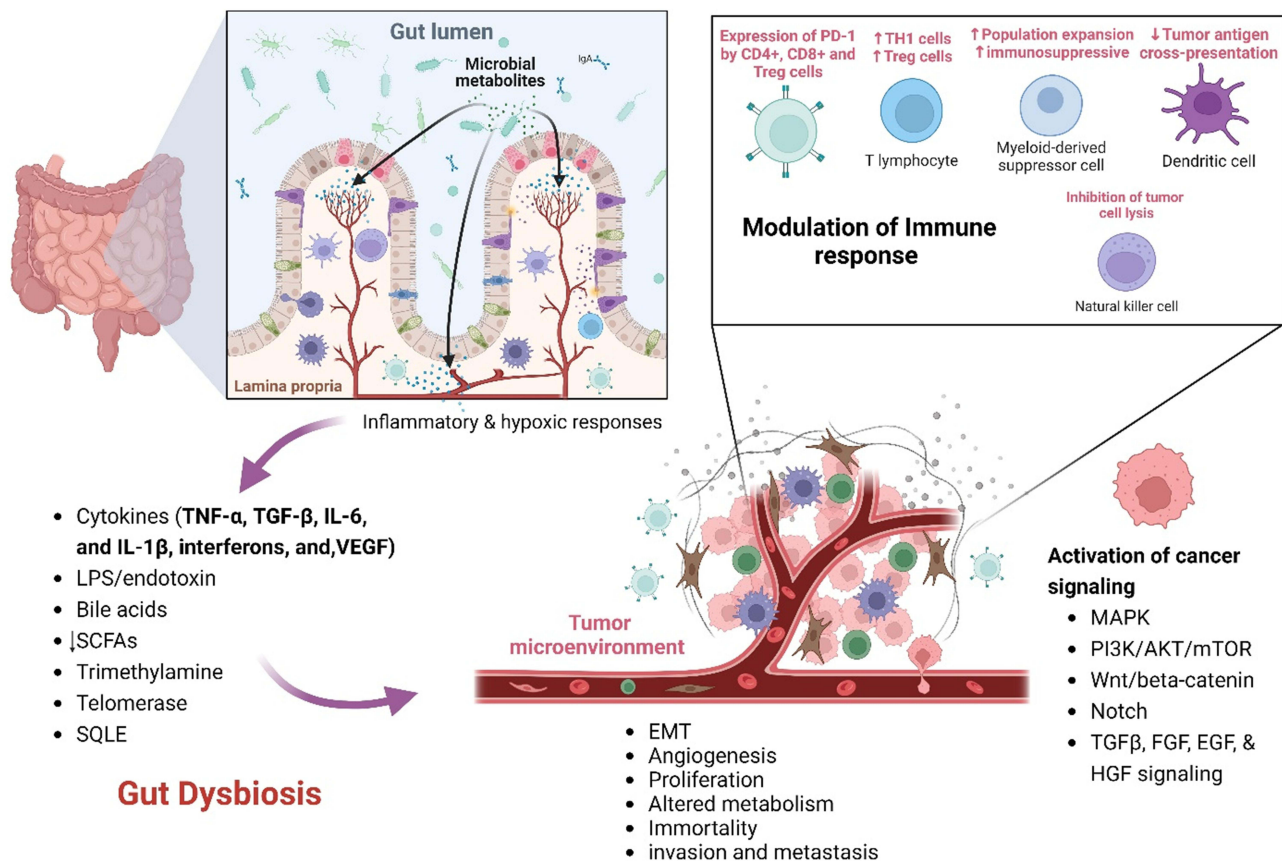


Figure 2 Mechanisms Linking Gut Dysbiosis to Cancer Progression; This illustration depicts the complex interplay between gut dysbiosis and cancer progression, highlighting how an imbalance in gut microbiota influences various cancer hallmarks. Gut dysbiosis alters microbial metabolite production, leading to enhanced signaling pathways that promote cancer cell proliferation and inhibit Tumor suppressor functions. Dysbiosis increases levels of pro-angiogenic factors such as VEGF, facilitating Tumor vascularization mediated by inflammatory cytokines (eg, TNF- α , IL-6) and microbial metabolites. Inflammatory responses triggered by gut dysbiosis degrade the extracellular matrix, aiding cancer cell invasion and metastasis. Gut dysbiosis affects nutrient absorption and metabolite availability, influencing cellular energy production and survival pathways in cancer cells. Dysbiosis also leads to an immunosuppressive Tumor microenvironment, achieved through modulation of T-cell function and immune checkpoint proteins, inhibition of natural killer cells and recruitment of myeloid-derived suppressor cells (MDSCs). Created in BioRender. Nabeel, W. (2025) <https://BioRender.com/y49m093>.

liver and colorectal cancer cells.⁵⁴ Certain pathogenic strains produce toxins like colibactin that induce DNA damage, disrupting cell cycle regulation and linking them to colorectal cancer.⁵⁵ Moreover, dysbiosis can lead to decreased levels of SCFAs like butyrate, which are crucial for promoting apoptosis in cancer cells.⁵⁶ Lower SCFA levels reduce apoptotic signaling, supporting cancer cell survival. Additionally, dysbiosis can influence cancer cell immortality by favoring bacteria that produce metabolites enhancing telomerase expression, thus extending cancer cell lifespan.⁵⁷

Studies in germ-free mouse models have demonstrated that the gut microbiome significantly impacts cancer onset and progression. For instance, overexpression of the enzyme SQLE has been shown to enhance colorectal cancer cell proliferation by promoting cell cycle progression and inhibiting apoptosis, with contributions from pathogenic bacteria.⁵⁸ Alterations in the microbiome associated with different stages of gastric cancer have highlighted specific bacteria as key players in disease progression. For example, infection with *Helicobacter pylori* initiates an inflammatory response, leading to the loss of acid-secreting cells and facilitating the colonization of other bacterial species, thus contributing to gastric carcinogenesis.⁵⁹ Non-*H. pylori* bacteria produce microbial metabolites like N-nitroso compounds and lactate, promoting cancer through mechanisms such as inflammation, immune modulation, DNA damage, and epithelial-mesenchymal transition (EMT).⁶⁰ Additionally, bacteria like *H. pylori* affect key cellular pathways, such as the AKT pathway, leading to deregulation of tumor suppressors and alterations in proliferative and survival pathways.⁶¹ Similarly, interactions with cellular structures like E-cadherin can disrupt cell junctions and activate oncogenic signaling pathways like β -catenin.⁶² Some bacteria, such as *Salmonella enterica*, can influence cell survival and proliferation by interacting with pathways like MAPK and AKT.⁶³ Pathogenic infections leading to dysbiosis can cause DNA damage and genomic instability, thereby initiating and advancing tumors in susceptible cells. Bacterial toxins like colibactin and cytolethal distending toxin (CDT) cause DNA breaks, leading to mutations and tumor development.⁶⁴ Additionally, pathogens like *Shigella flexneri* can disrupt DNA damage response and repair pathways, increasing mutation risks during DNA repair.⁶⁵

Inducing Angiogenesis

Tumor growth necessitates a blood supply, which is achieved through angiogenesis, the formation of new blood vessels. Dysbiosis can contribute to increased levels of pro-angiogenic factors such as vascular endothelial growth factor (VEGF), facilitating tumor vascularization. Studies have shown that certain gut bacteria can stimulate VEGF production, promoting angiogenesis in cancers like pancreatic cancer.⁶⁶ The relationship between gut dysbiosis and angiogenesis involves complex interactions where microbial imbalance influences inflammatory responses and biochemical signaling to support new blood vessel growth, which is essential for tumor development. Elevated levels of pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1 β , associated with dysbiosis, can increase VEGF expression and enhance angiogenesis in cancers like colorectal cancer.⁶⁷ Additionally, microbial metabolites such as secondary bile acids can induce angiogenesis, impacting liver cancers like hepatocellular carcinoma by promoting liver inflammation and tumor vascularization.⁶⁸ Dysbiosis also impairs intestinal barrier function, allowing substances like lipopolysaccharides (LPS) to enter the bloodstream and trigger systemic inflammation and angiogenesis, particularly relevant to pancreatic cancer progression through PI3K/AKT signaling.^{69,70} The altered immune landscape due to dysbiosis, marked by reduced immune surveillance and increased immunosuppression, supports an angiogenic environment that aids malignancies like gastric cancer.⁷¹ These insights suggest potential therapeutic approaches, including probiotics, prebiotics, dietary interventions, and targeted therapies aimed at modulating the gut microbiota, reducing inflammation, and inhibiting angiogenic pathways in cancer treatment.

Activating Invasion and Metastasis

The ability of cancer cells to invade surrounding tissues and metastasize to distant sites is a critical hallmark of cancer.⁵³ This complex process involves several steps: detachment from the primary tumor, acquisition of an invasive phenotype through epithelial-mesenchymal transition (EMT), local invasion, intravasation into the circulatory system, systemic transportation, extravasation, and colonization in secondary organs.⁷² Microbial imbalance in the gut can promote inflammation, facilitating extracellular matrix degradation and cancer cell spread. For example, *Fusobacterium nucleatum* has been associated with enhanced metastatic potential in colorectal cancer by binding to cancer cells and

promoting invasion.⁷³ Circulating tumor cells (CTCs) typically arise from epithelial tumor cells that have undergone EMT, marked by loss of adhesion and polarity, cytoskeletal reorganization, acquisition of tumor stem cell properties, and resistance to therapy. EMT is regulated by transcription factors such as Snail 1, Slug, ZEB1, Twist, and FOXC2, and influenced by tumor microenvironment signaling pathways like WNT, Notch, Hedgehog, TGF β , FGF, EGF, and HGF.^{74,75} Tumor hypoxia further activates signaling pathways like PI3K, WNT/ β -catenin, and MAPK, crucial for regulating EMT.⁷⁶ Gut dysbiosis significantly impacts this process by altering the tumor microenvironment, supporting systemic inflammation, and modulating immune responses, thus creating conditions favorable for tumor cell invasion and metastasis. Dysbiosis can also affect the production of cytokines and growth factors, influencing cancer cell metastatic potential.⁷⁷ Before arriving at the premetastatic niche, VEGFR1-positive hematopoietic progenitor cells migrate from the bone marrow into the circulation and establish in secondary organs, where they adhere to fibronectin produced by fibroblasts. This process is mediated by integrin VLA-4 and influenced by chemokine SDF-1 binding to the CXCR4 receptor on breast cancer cells, particularly associated with bone metastasis.⁷⁸ Gut dysbiosis enhances systemic inflammation, increasing pro-inflammatory cytokines and stimulating overproduction of growth factors like VEGF-A, FGF1, EGF, and PDGF, which further support angiogenesis and metastasis. Metabolic byproducts of dysbiosis can also modulate angiogenic factor expression through signaling pathways within cancer cells. Additionally, exosomes released by cancer and immune cells, carrying proangiogenic molecules, play a role in tumor angiogenesis and metastasis, with gut dysbiosis potentially altering their composition and function.^{79,80} This intricate interaction between gut microbiome dysregulation and the tumor microenvironment underscores the systemic effects of gut health on cancer progression and metastasis, highlighting the need for a balanced gut microbiome in cancer prevention and treatment.

Deregulating Cellular Energetics

Cancer cells often exhibit altered metabolism, known as the Warburg effect, where they preferentially use glycolysis over oxidative phosphorylation for energy production, even under normoxic conditions. Gut dysbiosis impacts cancer cell metabolism, particularly in colorectal and pancreatic cancers, by affecting nutrient absorption and metabolite availability. In colorectal cancer, dysbiosis disrupts normal fermentation processes, impacting SCFA production like butyrate, which can be utilized by hypoxic tumor cells to support survival and proliferation.⁸¹ This process is mediated through the activation of the butyrate receptor GPR109A, which modulates the NF- κ B pathway and influences inflammatory responses and cell survival.⁸² Dysbiosis also affects the synthesis of amino acids and the conversion of primary bile acids into secondary bile acids. These secondary bile acids have been implicated in DNA damage and the activation of carcinogenic signaling pathways, particularly through the FXR and TGR5 receptors in the liver and colorectal cancers.^{83,84}

In pancreatic cancer, dysbiosis exacerbates the reliance of cancer cells on alternative energy sources, such as amino acids and lipids. This metabolic reprogramming, often referred to as the Warburg effect, illustrates the cancer cells' preference for glycolysis, which results in the accumulation of glycolytic intermediates used as building blocks and an increased production of lactic acid.^{70,85} Lactic acid modulates the tumor microenvironment by suppressing immune surveillance and promoting angiogenesis through the activation of HIF-1 α , which enhances the expression of vascular endothelial growth factor (VEGF).

Hypoxia, a common feature in solid tumors like pancreatic adenocarcinoma, activates hypoxia-inducible factors (HIFs) that upregulate glucose transporters (such as GLUT1) and glycolytic enzymes (including HK2 and PFKFB3), boosting glucose uptake and metabolism.^{86,87} HIFs also play a role in stimulating angiogenesis by upregulating VEGF, contributing to the tumor's growth and metastatic potential.⁸⁸ Dysbiosis can aggravate these hypoxic responses by promoting systemic inflammation through the release of microbial metabolites that mimic host signaling molecules, further influencing metabolic adaptations in cancer cells.

Avoiding Immune Destruction

The immune system plays a crucial role in identifying and eliminating cancer cells. However, gut dysbiosis can lead to an immunosuppressive tumor microenvironment that diminishes the efficacy of immune surveillance. For example, certain bacteria can modulate T-cell function or influence the expression of checkpoint proteins, which cancer cells exploit to

evade immune detection. This intricate interplay between gut microbiota and immune responses significantly influences cancer progression, especially in colorectal cancer, hepatocellular carcinoma, and melanoma.

In colorectal cancer, the gut microbiota's role is highlighted through its ability to modulate the immune landscape via cytokine signaling and T helper cell differentiation. Transplantation of microbiota from CRC patients into mice has shown to induce colorectal tumorigenesis, mediated through the elevation of pro-inflammatory cytokines such as interleukin-17 (IL-17) and interferon-gamma (IFN- γ), which enhance Th1 and Th17 cell infiltration in the colon.⁸⁹ These conditions promote inflammatory and oncogenic pathways in the intestinal epithelium.

Specific pathogens such as *Fusobacterium nucleatum* facilitate CRC progression by recruiting myeloid-derived suppressor cells (MDSCs) and inhibiting natural killer (NK) cells and T cells through mechanisms involving the engagement of the TIGIT receptor, which inhibits NK cell cytotoxicity.⁹⁰ Research reveals that *Peptostreptococcus anaerobius* is significantly more abundant in stool samples and colon biopsies from patients with colorectal cancer (CRC) and advanced adenoma than in those from healthy controls.⁹¹ This bacterium predominantly colonizes the colon and stimulates cell proliferation by interacting with TLR2 and TLR4 receptors on colon cells, leading to increased reactive oxidative species which enhance cholesterol synthesis, driving cell proliferation.

Hepatocellular Carcinoma (HCC): In HCC, the gut-liver axis is critical, with gut microbiota-derived metabolites and endotoxins like lipopolysaccharide (LPS) exacerbating liver pathology. LPS activates the NF- κ B signaling pathway in hepatic stellate and Kupffer cells, leading to inflammation and fibrogenesis.⁹² Dysbiosis also affects bile acid metabolism, increasing the production of oncogenic secondary bile acids.⁹³ Additionally, the decrease in beneficial microbes such as *Akkermansia muciniphila* and the presence of specific bacteria like *Clostridium* species are linked to increased MDSC infiltration and reduced levels of hepatic CXCR6⁺ natural killer T cells, respectively, which collectively dampen antitumor immunity.^{94,95}

Melanoma: In melanoma, gut microbiota composition can significantly alter the efficacy of immunotherapies. Certain bacteria affect the responsiveness to checkpoint inhibitors by influencing the immune checkpoint axis, altering the expression of CTLA-4 and PD-1 on T cells.⁹⁶ Skin microbiota also play a role by producing antimicrobial peptides and modulating cytokine profiles, such as increasing IL-17 production, which can affect immune surveillance and influence melanoma progression.⁹⁷

These examples underscore the profound impact of gut microbiota on immune system function across various cancers. By modulating cytokine production, influencing immune cell differentiation, and interacting with metabolic pathways, gut microbiota can shape the tumor microenvironment, promoting immune evasion and cancer progression. Targeting microbial communities to restore a balanced gut microbiome offers a promising strategy for enhancing immune response and improving outcomes in cancer therapy.

Gut Microbiota Translocation

Introduction to Gut-Liver Axis and Disease

Previous research has highlighted the significant role of gut microbiota in diseases such as colorectal cancer, liver diseases, and particularly hepatocellular carcinoma (HCC). The liver is intricately connected to the gut via the portal vein, serving as a primary pathway for substances absorbed in the gut to reach the liver. Thus, any increase in intestinal permeability can facilitate the translocation of gut microbiota and their metabolites to the liver, potentially influencing liver health and disease progression.

In patients with hepatocellular carcinoma, metabolites from gut microbiota such as lipopolysaccharides (LPS) have been shown to trigger inflammation and liver injury, which in turn promote hepatocarcinogenesis.⁸⁸ Additionally, dysregulation of bile acids by gut microbiota has been identified as a contributing factor to liver cirrhosis and cancer. Recent research in HCC has noted an increase in LPS-producing microbiota in patients with liver cirrhosis-HCC, while butyrate-producing microbiomes are decreased.⁸⁸ Bile acids are crucial for maintaining liver health, and alterations in bile-acid-associated microbiota can significantly impact liver metabolism. For instance, Lithocholic acid, a secondary bile acid derived from the dehydroxylation of chenodeoxycholic acid (CDCA), has been found to be hepatotoxic and increases the risk of developing HCC.⁹⁸

Gut Microbiota and Colorectal Cancer

A recent nested case-control study has further explored the connection between gut microbiota and colorectal cancer (CRC) through the analysis of circulating biomarkers related to gut microbiome activity. This study involved 261 CRC patients and 261 controls, monitored over a follow-up period of up to 15 years. Biomarkers such as LPS-binding protein (LBP), soluble CD14 (sCD14), and endotoxin core antibody (EndoCAb) immunoglobulin M (IgM) were measured to assess their association with CRC incidence. The results indicated a positive association between sCD14 levels and the incidence of CRC, suggesting that sCD14 could be a marker of microbial translocation and subsequent immune activation.⁹⁹ These biomarkers are initiated primarily through the translocation of microbial lipopolysaccharides, which result in gut barrier dysfunction. Factors such as alcohol consumption and a high-fat diet are known to compromise gut barrier integrity. Upon reaching the gut barrier, LPS can bind to the cell surface Toll-like receptor 4 (TLR4) via the MD2-TLR4 complex, activating the production of inflammatory cytokines that stimulate the immune response. However, the EndoCAb was found to have a low association with CRC incidence, indicating variable impacts of different biomarkers.⁹⁹ Thus, this dysfunction of the gut barrier alters the balance between commensal and deleterious bacteria in the gut microbiota, leading to the activation of inflammatory cytokines and prolonged inflammation that targets the epithelial colorectal cells, potentially culminating in CRC. The study underscores the importance of maintaining gut barrier integrity to prevent the adverse effects of microbial translocation on liver and colorectal health. This highlights the need for targeted interventions that could modulate gut microbiota to prevent or mitigate the progression of liver-related diseases and colorectal cancer.

Clinical Value of Gut Microbiota in Cancer Prognosis and Treatment

The gut microbiome is a stable, diverse component of the human body that is closely linked to individual health. Factors such as genetics, diet, environment, medications, and smoking can cause variations in the gut microbiome, distinguishing drug responders from non-responders.^{100,101} The gut microbiome interacts with the immune system, influencing the differentiation of lymphocytes, NK cells, and Tregs, which suggests its potential as a predictor of immunotherapy efficacy. Stool samples provide easy access to gut microbiome data, enabling clinicians to gather baseline information before treatment. Several studies have shown that the baseline gut microbiome composition can serve as a promising predictor of immunotherapy response.

Specific gut bacteria have been associated with improved outcomes in cancer treatment. For example, the presence of *Akkermansia muciniphila* has been linked to enhanced efficacy of PD-1 blockade in lung, liver, and kidney cancer patients.^{93,102,103} This bacterium is thought to modulate the immune system by boosting the recruitment and activation of immune cells, particularly CD8⁺ T cells, which are essential for antitumor immunity.¹⁰⁴ Similarly, *Bifidobacterium* has been associated with better outcomes in melanoma patients receiving anti-PD-L1 therapy.¹⁰⁵ *Bifidobacterium spp.* promotes the maturation and function of dendritic cells, leading to a stronger T-cell response against tumors.¹⁰⁶ Beyond specific bacterial species, the overall diversity of the gut microbiome is a significant predictor of cancer prognosis. A more diverse microbiome supports a balanced immune system, reduces chronic inflammation, and promotes effective antitumor responses. Patients with higher gut microbiome diversity have shown better progression-free survival (PFS) and overall survival (OS) in cancers such as melanoma and non-small cell lung cancer (NSCLC).^{107–109}

While immunotherapy activates the immune response, it can also lead to immune-related adverse events (irAEs). Predicting these adverse events, particularly severe ones, is crucial for preventing complications and optimizing treatment. Interestingly, molecular markers like PD-L1 expression levels may not reliably predict irAEs, as a Phase 3 clinical trial found similar irAE rates in NSCLC patients regardless of PD-L1 expression.¹¹⁰ However, the gut microbiome plays a more substantial role in predicting irAEs.

The gut microbiome can act as both a risk and protective factor for irAEs. Checkpoint inhibitor colitis (CIC) is one of the most common irAEs. *Faecalibacterium prausnitzii* is considered a risk factor for CIC, while *Bacteroides fragilis*, with its anti-inflammatory properties, acts as a protective factor in the gastrointestinal tract.^{111,112} Enrichment of *Bacteroidetes*, which promotes Treg differentiation, has been linked to resistance against CIC development.¹¹² In liver

cancer, reduced gut microbiome diversity and abundance were associated with severe immunotherapy-related colitis, suggesting that the microbiome can predict both the occurrence and severity of irAEs.¹¹³

In metastatic melanoma patients treated with Ipilimumab, a higher abundance of *Faecalibacterium* and other *Firmicutes* correlated with improved responses (longer PFS and OS) but also increased colitis risk, with fewer Tregs in peripheral blood.¹¹⁴ This indicates that specific bacteria can predict both immunotherapy efficacy and the likelihood of irAEs. The gut microbiome may also predict other irAEs such as diarrhea and skin toxicity. *Prevotellamassilia timonensis*, a biomarker for severe colitis in liver cancer patients, has also been linked to severe diarrhea.¹¹⁵ In advanced NSCLC patients, reduced gut microbiome diversity was associated with higher rates of skin toxicity during immunotherapy.¹¹⁶ A prospective cohort study (NCT03688347) found that bacteria such as *Bifidobacterium* and *Desulfovibrio* could predict overall irAE risk rather than specific irAE types.¹¹⁷ Neoadjuvant immunotherapy is becoming an increasingly popular treatment option for cancer patients. In esophageal squamous cell carcinoma (ESCC) patients receiving neoadjuvant camrelizumab and chemotherapy, taxonomic features of the gut microbiome were found to predict both pathological responses and severe adverse events (grade ≥ 3)¹¹⁸ expanding the potential applications of microbiome biomarkers in cancer prognosis.

Gut Microbiota Disparities in Treatment Outcomes

Interactions With Immune Checkpoint Inhibitors (ICIs)

The interaction of cancer cells with the immune system primarily occurs through T cells, which identify cancer antigens presented by Major Histocompatibility Complex class I (MHC I) as in demonstrated in Figure 3A. While immune checkpoints

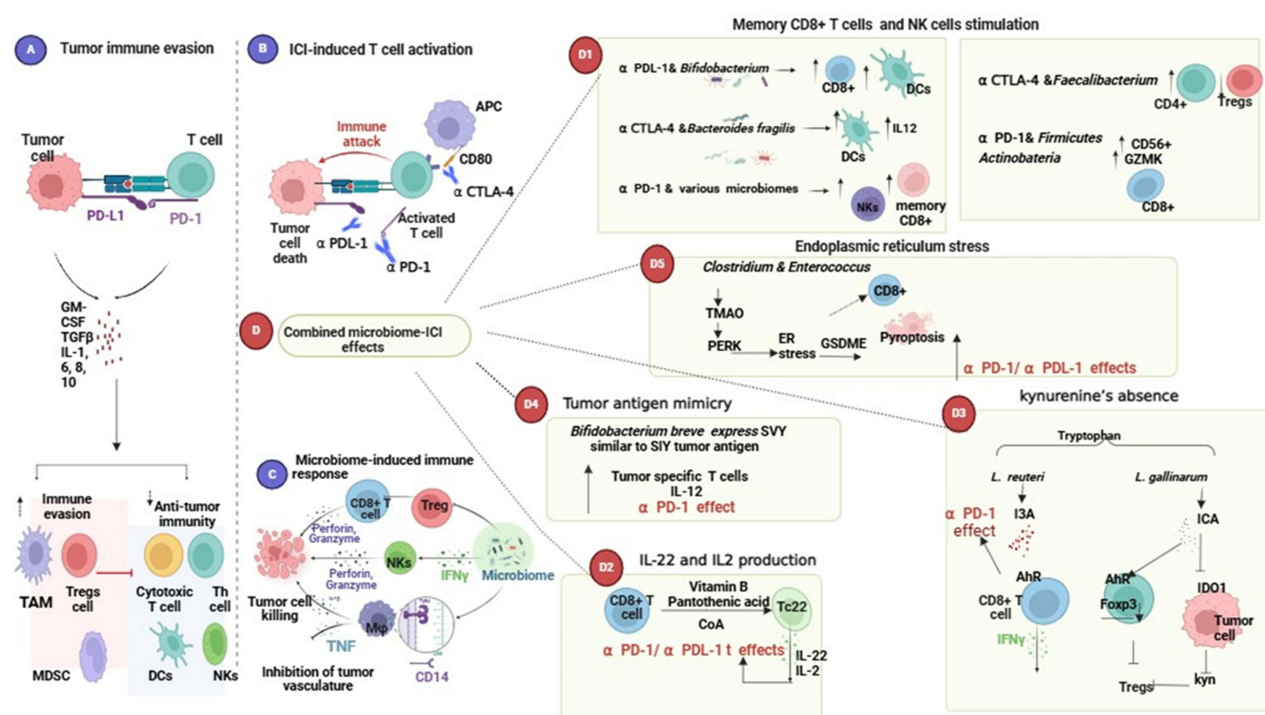


Figure 3 The combination of microbiomes with immune checkpoint inhibitors in cancer therapy produces a wide range of meaningful effects. **(A)** Immune checkpoints like PD-L1 inhibit T-cell activation. Tumor cells use the PD-1-PD-L1 link to evade the immune response by stimulating the development of regulatory cells that prevent the activation of T helper and cytotoxic T cells. **(B)** Anti-PD-1/anti-PD-L1/anti-CTLA4 antibodies promote T cell activation by inhibiting immunological checkpoints between tumor and T cells. **(C)** Microbiomes promote the anti-immune response by stimulating natural killer cells via IFN gamma and inhibiting Regulatory T cells (Tregs) activation, resulting in tumor death. **(D)** Microbiomes communicate with immunological checkpoints through several methods. **(D1)** *Bifidobacterium* plus anti-PD-L1/ *Bacteroides fragilis* plus anti-CTLA4 / great diversity of microbiomes plus anti-PD-1 enhances memory cell formation CD8⁺ T cells and natural killer cells work together to stimulate both the innate and adaptive immune systems, improving the efficiency of ICI by upregulating dendritic cells and T helper cells. **(D2)** Microbiome-derived vitamin B induces the development of IL-22 and IL-2 generating TC 22 cells, which improves the efficacy of anti-PD-1 and anti-PD-L1. The ICA from *L. gallinarum* enhanced anti-PD-1 therapy by reducing IDO1 expression and kynurenine synthesis. *L. reuteri* improved ICIs by promoting CD8⁺ T cell growth and IFN-gamma release. **(D3)** *B. breve* expresses SVY, mimicking tumor antigens and stimulating the immune response by upregulating IL-12 and activating tumor-specific T cells. **(D4)** *Bifidobacterium breve* expresses SVY, which mimics tumor antigens and induces an immune response to tumors by upregulating IL-12 and activating tumor-specific T cells. **(D5)** *Clostridium* and *Enterococcus*-derived TMAO produce stress in the endoplasmic reticulum, which leads to tumor cell death via CD8⁺ T cells and pyroptosis. Created in BioRender. SaBÅ0. (2025)h tps://BioRender.com/s51t086.

and co-stimulatory molecules limit the immune response to prevent autoimmunity, they also allow tumors to evade immune destruction as shown in [Figure 3B](#). Tumor-infiltrating lymphocytes interact with Tumor antigens via the PD-1/PD-L1 signaling pathway. The combination of PD-L1 and PD-1 sends inhibitory signals that limit T cell growth and activation, allowing Tumor immune evasion and distant metastases as shown in [Figure 3C](#). Anti-PD-1 or anti-PD-L1 therapies, on the other hand, may minimize Tumor cell evasion while enhancing immune responses; inhibiting immunological checkpoints between T cells and malignant cells increases the number of activated T cells capable of recognizing and killing Tumor cells ([Figure 3D](#)).¹¹⁹ These therapies have shown significant success in treating diseases such as lung cancer¹²⁰ and malignant melanoma,¹²¹ despite challenges related to immune resistance at various treatment stages.¹⁰⁰

Microbiota's Role in Immune Modulation

Research has increasingly focused on the role of gut microbiota in cancer development and modulating immune responses during infections and cancer. Animal studies have examined the impact of ICIs on the translocation of specific gut microbiomes to secondary lymph nodes and tumors, exploring tumor-draining lymph nodes (TDLNs), primary tumors, and mesenteric lymph nodes (MLNs).¹²² For example, in studies involving melanoma treated with a combination of anti-PD-1 and anti-CTLA4, a higher abundance of bacteria was observed in the MLNs of treated groups compared to untreated groups, highlighting the significant influence of ICIs on gut microbiota dynamics.¹²² These studies suggest that ICIs may enhance the translocation of microbiota via dendritic cells, which are recruited into secondary lymphoid organs in association with CCR7, activating a potent anti-tumor immune response, especially involving CD8+ T cells.

Influence on Lymphocyte Relocation and Immunotherapy Efficacy

Recent research has demonstrated that the gut microbiota substantially affects the efficacy of immunotherapy by influencing the relocation of lymphocytes within the ileal lumen. For instance, a study showed that the commensal microbiome preserves immune cells in the ileal lamina propria and MLNs, where high endothelial venules express adhesion molecules like Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1).¹²³ These molecules interact with $\alpha 4\beta 7$ integrin on lymphocytes, including regulatory T cells (Tregs) and T helper cells, enhancing tumor control while avoiding disruptions by ICIs.

Conversely, antibiotics and dysbiosis can disrupt MAdCAM-1 interactions, forcing Tregs and T helper cells to migrate to tumor microenvironments, potentially accelerating tumor growth. For instance, a particular strain of *Enterocloster*, including *E. clostridioformis*, has been shown to down-regulate MAdCAM-1, influencing T cell positioning and activity.¹²³

Case Studies and Clinical Outcomes

Fecal microbiota transplantation (FMT) combined with anti-PD-1 therapy has been observed to reverse immunological resistance to PD-1 and improve the tumor microenvironment (TME) in melanoma research.¹²⁴ Patients responding to treatment exhibited a higher presence of specific T cell subsets, and the modification of the gut microbiome through FMT influenced responses to PD-1 blockade.

Additionally, a comprehensive study assessed the contribution of gut microbiota in patients with non-small cell lung cancer and metastatic colorectal cancer. The presence of butyrate-producing bacteria correlated with improved progression-free survival, highlighting the potential of targeting gut microbiota to enhance the outcomes of immunotherapy.¹²⁵

Ongoing Research

A cohort study involving 175 metastatic melanoma patients receiving ICI therapy is currently underway to profile the gut microbiota and its correlation with treatment outcomes.¹²⁶ This study is examining the microbiota's association with monotherapy, combination therapy, and ICI-related side effects like colitis. Initial findings suggest that specific microbial patterns, such as the abundance of SCFA producers or certain Clostridia species, may correlate with progression-free survival and immune-related adverse effects. These investigations (demonstrated in [Table 1](#)) underline the critical role of gut microbiota in modulating immune responses and influencing the efficacy of cancer therapies, paving the way for

**Table 1** Microbiomes Modulating the Impact of Immune Checkpoints in Cancer

Cancer	ICI	Common Microbiome	Outcome; PFS/iRAE	Ref.
mCRC	CETUXIMAB (anti-EGFR)& AVELUMAB (anti- PD-L1)	<i>Agathobacter</i> M104/I <i>Blautia</i> SR1/5	ICI with <i>Agathobacter</i> M104/I improves m CRC patients PFS from 4.6 to 13.5 months, while <i>Blautia</i> SR1/5 raises it from 3.6 to 5.9 months	[114]
Chemo-refractory nonsmall cell lung cancer	CETUXIMAB& AVELUMAB	<i>Agathobacter</i> M104/I <i>Blautia</i> SR1/5	ICI with <i>Agathobacter</i> M104/I increases chemo - refractory NSCLC patient PFS from 1.4 to 7.8 months, while <i>Blautia</i> SR1/5 raises it from 1.8 to 7.8 month.	[114]
mRCC	Nivolumab (anti- PD-I) &IPILIMUMAB (anti- CTLA4)	CBM588: bifidogenic bacterial product	ICI with bifidogenic bacterial product raises RCC patients' PFS from 2.5 to 12.7 months.	[117]
Meta-analysis Lung cancer, melanoma & multi	Anti PD I Anti- PDL- I Anti CTLA4 Combined ICI s	Menaquinone-derived microbiome, <i>Parabacteroides goldsteinii</i> <i>Parabacteroides merdae</i> , <i>Ruminococcus</i>	Menaquinone-derived microbiome predicts ICI efficacy in lung cancer and melanoma, with lower expression in irAF patients than non-irAFs	[116]
Refractory melanoma	Anti-PD-1PEMBROLIZUMAB	<i>Actinobacteria</i> ; <i>Bifidobacteriaceae</i> spp., <i>Coriobacteriaceae</i> , <i>Firmicutes</i> & <i>Ruminococcaceae</i> . <i>Lachnospiraceae</i>	ICI combined with microbiomes extends PFS by up to 7 months in refractory melanoma patient	[113]
Advanced melanoma	AntiPD; NIVOLUMAB or PEMBROLIZUMAB	<i>Bacteroides</i> species (except for <i>B. intestinalis</i>) a <i>Coprococcus eutactus</i>	<i>Bacteroides</i> monotherapy in advanced melanoma patients led to a PFS ≤ while with <i>Coprococcus eutactus</i> the PFS ≥ 12 months combined ICI with <i>Coprococcus eutactus</i> and <i>Butyricoccus</i> declined PFS ≤ 12 months	[115]
	NIVOLUMAB or PEMBROLIZUMAB combined IPILIMUMAB).	<i>Coprococcus eutactus</i> <i>Butyricoccus</i> sp.		

Abbreviations: mCRC, Metastatic colorectal cancer; RCC, Metastatic renal cell cancer; irAFs, Immune-related adverse effects; FMT, fecal microbiota transplant; EGFR, Epidermal growth factor receptor.

novel therapeutic strategies that integrate microbiome modulation with conventional treatments to enhance patient outcomes.

Mechanisms Underlying the Interaction Between Gut Microbiota and ICI's Efficacy

Microbiota-Driven Activation of Innate Immunity: Mechanistic Insights for Immune Checkpoint Inhibitors

The gut microbiota plays a pivotal role in augmenting the response to immune checkpoint inhibitors (ICIs) by activating various components of the innate immune system. For instance, *Bifidobacterium* enhances the anti-cancer efficacy of ICIs by stimulating dendritic cells, which increases CD8+ T cell activity and helps overcome PD-L1 resistance.³ Similarly, *Bacteroides fragilis* not only prompts dendritic cell maturation and IL-12 activation, enhancing anti-CTLA-4 antibody efficacy, but also stimulates macrophage polarization to M1, bolstering innate immunity.³ Furthermore, the microbiota induces interferon gene stimulators and IFN signaling, which facilitates the transition from innate to adaptive immunity, converting mononuclear phagocytic cells into anti-tumor macrophages and activating the NKs-DCs axis.^{127,128}

Microbiota-Driven Activation of Adaptive Immunity: Mechanistic Insights for Immune Checkpoint Inhibitors

The gut microbiota significantly influences the efficacy of ICIs across various cancer types by modulating adaptive immune responses. In melanoma, the presence of microbes such as those from the *Clostridiales*, *Ruminococcaceae*, and *Faecalibacterium* families enriches the tumor microenvironment (TME), enhancing antigen presentation to dendritic cells

and boosting effector CD4⁺ and CD8⁺ T cell responses.³ Clinical trials involving fecal microbiota transplantation (FMT) have shown that the enrichment of *Firmicutes* and *Actinobacteria* can amplify PD-1 inhibition to enhance anti-tumor responses.¹²⁴

Microbiota-Driven Metabolic Modulation of ICIs

Gut microbiota produces a myriad of metabolites that influence the immune response, particularly during ICI treatment. Metabolites such as short-chain fatty acids (SCFAs), inosine, and trimethylamine N-oxide (TMAO) have shown significant interactions with ICIs, boosting anti-tumor immune responses.³ For instance, *Clostridium* and *Enterococcus*-produced TMAO can cause ER stress leading to gasdermin-E-mediated pyroptosis, thereby enhancing CD8⁺ T cell functionality in the anti-tumor response.^{129,130} Additionally, SCFAs like propionic acid, produced by *A. muciniphila*, disrupt tumor cell proliferation and enhance ICI effects by inhibiting apoptosis.

Translocation and Immune Cell Recruitment in the TME

Recent studies have explored how the translocation of specific microbiota influences immune cell dynamics within the TME. For instance, *Lactobacillus reuteri* has been found to migrate to tumor sites, releasing metabolites like indole-3-aldehyde (I3A) from dietary tryptophan, which modulates the immune response by activating the aryl hydrocarbon receptor (AhR) on CD8⁺ T cells and promoting TC1 differentiation.^{131–133} This activation facilitates the production of IFN γ by CD8⁺ T cells, enhancing the anti-tumor immune response and potentially prolonging progression-free survival (PFS) in melanoma patients under ICI therapy.^{134–136}

Influence of Gut Microbiota on Tumor Immunogenicity and ICI Efficacy

Gut microbiota can provoke tumor immunogenicity, enhancing ICI efficacy by producing tumor-cross antigens that activate anti-tumor immunity. An illustrative example is *Bifidobacterium breve*, which expresses an antigen similar to a tumor antigen found in melanoma cells, leading to T cell-mediated tumor cell destruction.¹³⁷ Additionally, microbiota-derived metabolites like inosine have been shown to sensitize tumor cells to T-cell cytotoxicity, highlighting a novel mechanism through which microbiota can influence the efficacy of ICIs.¹³⁸ The interactions between gut microbiota and ICIs illustrate a complex network involving innate and adaptive immunity, metabolic modulation, and direct impacts on the TME. This intricate relationship underscores the potential of leveraging gut microbiota in enhancing the efficacy of cancer immunotherapies, offering promising avenues for future research and therapeutic strategies.

Microbiome-Based Therapeutics to Improve Immune Checkpoint Inhibitors Efficacy

Fecal Microbial Transplantation (FMT)

Intensive chemotherapy often disrupts gut microbiota composition, leading to dysbiosis. Fecal microbial transplantation (FMT) has emerged as a novel approach to restore the gut microbiota during disease treatment. In acute myeloid leukemia (AML) patients, microbiota dysbiosis due to chemotherapy and antibiotics has been observed. A Phase II clinical study revealed that autologous fecal microbiota transfer (AFMT) is a safe and effective method for re-establishing gut microbiota, compared to traditional FMT.¹³⁹ Ongoing studies, including a randomized clinical trial (NCT04758507) with advanced renal cell carcinoma patients, are exploring the significant role of gut microbiota in modulating the effectiveness of immune checkpoint inhibitors.² Further research using FMT capsules in gastrointestinal cancer aims to counteract resistance to ICIs, particularly anti-PD-1 treatments. Recent trials, such as one involving advanced melanoma patients (NCT03772899), reported a 65% response rate using FMT in combination with PD-1 inhibitors like nivolumab or pembrolizumab, achieving up to a 20% complete response rate.¹⁴⁰ Another phase II trial (ChiCTR2100046768) documented improved survival in treating refractory microsatellite stable metastatic colorectal cancer using a combination of FMT with anti-PD-1 inhibitors, highlighting the importance of specific bacterial populations such as *Proteobacteria* and *Lachnospiraceae* in responders.¹⁴¹

Dietary Interventions

Diet plays a crucial role in modulating tumor immunity. For instance, a high salt diet has been found to promote the translocation of Bifidobacterium into the tumor microenvironment (TME), enhancing NK cell activity and anti-tumor immunity.³ A nested case-control study linked dietary metabolites like choline, betaine, and phenylacetylglutamine (PAGIn) with lethal prostate cancer, suggesting that microbiota-related metabolites produced from specific diets influence cancer progression.¹⁴² Additionally, the traditional herbal remedy Xiao-Chai-Hu-Tang (XCHT) has been studied for its antidepressant properties and potential to influence cancer treatment. A xenografted mouse model of colorectal cancer treated with XCHT under chronic restraint stress showed increased longevity and modified levels of specific gut bacteria, which may suppress TLR4/MyD88/NF- κ B signaling involved in tumor growth.¹⁴³

Probiotics and Prebiotics

Probiotics are used to support disease treatment by restoring microbiota balance. Recent studies highlight the beneficial role of *Clostridium butyricum* in post-gastrectomy gastric cancer patients. This probiotic promotes gut microbiota regeneration, enhancing immune function and reducing inflammation through metabolites like butyric acid, which also helps in regenerating host intestinal epithelial cells.¹⁴⁴

Prebiotics, indigestible food ingredients that promote the growth of beneficial gut bacteria, have also shown promise. In a Phase I clinical trial (NCT05303493), the prebiotic camu camu influenced the growth of health-promoting gut bacteria like *Ruminococcus bromii* in advanced melanoma patients experiencing immune-related adverse events (irAEs) from ICIs. This intervention appeared to minimize irAEs and enhance the immune response.^{145,146}

Future Directions

This review has underscored the complex interplay between gut microbiota, its metabolites, and immune checkpoint inhibitors. The dynamic interactions suggest the need for further research to uncover the underlying mechanisms of this modulatory effect and investigate distinct microbiota compositions that may improve immunotherapy outcomes. Personalized microbiota modification methods, advanced spatial multi-omics tools, and targeted metabolomics analysis are crucial for optimizing therapeutic efficacy and understanding individual variability in response to cancer treatments. Moreover, monitoring the microbiota throughout treatment could provide insights into how microbiome composition affects treatment efficacy and patient outcomes, paving the way for personalized medicine in cancer management.

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Disclosure

The authors declare that they have no competing interests in this work.

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