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GUT MICROBIOTA AND SYSTEMIC IMMUNITY: MECHANISMS LINKING MICROBIAL SIGNALS TO INFLAMMATION AND IMMUNOTHERAPY RESPONSE

Razia Iqbal[*1], Shahid Mahmood[*2], Rimsha Aslam[3], Noor-Ul-Ain[4], Tehreem Zafar[5], Bareera Amjad Iqbal Ahmad[6]

[*1,*2, 3,4,5,6] *Department of Zoology, University of Gujrat, Gujrat 50700, Pakistan*

[*1]razia.iqbal@uog.edu.pk, [*2]shahid.mahmood@uog.edu.pk

Corresponding Author: *
Razia Iqbal ,
Shahid Mahmood

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ABSTRACT

The gut microbiome is a complex microbial bionetwork that constantly modulates the immune system of the host. This interaction is responsible for controlling systemic inflammation and directing the course of immunity in various diseases. This review summarizes the present data on microbiome-immune system interactions, with a special emphasis on microbiome effects in inflammation and immunotherapy. Multiple molecular pathways enable the gut microbiome to influence host immune function. Gut microbial byproducts, including tryptophan derivatives, Short-Chain Fatty Acids, and bile acids, influence phagocytic cell development in addition to cytokine production. Structural components such as lipopolysaccharides activate pattern-recognition receptors and drive systemic inflammatory signaling. Dysbiosis reduces beneficial commensal taxa and increases microbial translocation. This disrupts intestinal barrier integrity and promotes chronic, low-grade inflammation linked to metabolic, autoimmune, and oncological conditions. Clinical evidence demonstrates that gut microbial composition significantly influences cancer immunotherapy end results. In melanoma, hepatocellular carcinoma, and non-small cell lung cancer, increased microbial heterogeneity and enrichment of specific taxa correlate with improved efficacy of Immune Checkpoint Inhibitors. Fecal Microbiota Transplantation studies provide causal evidence that microbiome composition can determine immunotherapy responsiveness. Specific microbial profiles also associate with immune-driven toxicities, such as checkpoint inhibitor-associated colitis. Dietary modification, probiotics, prebiotics, and synbiotics collectively represent potential interventions to reconstitute microbial homeostasis as well as improve immune outcomes. However, substantial challenges remain, including inter-individual variability, limited methodological standardization, and difficulty establishing causality in observational studies. Future research integrating multi-omics approaches may enable microbiome-based biomarkers and personalized immunotherapy strategies.

Keywords: *Gut microbiota, microbiome-immune crosstalk, systemic inflammation, dysbiosis, antitumor immunity, intestinal barrier function, regulatory T cells, microbial diversity, and immunotherapy*

INTRODUCTION

The gut microbiota of humans is a multifaceted environment composed of archaea, fungi, viruses, and bacteria that plays a pivotal part in immune response modulation (Schluter et al., 2020; Gopalakrishnan et al., 2018). The estimated bacterial count is 3.8×10^{13} (Chang et al., 2024). The gut microbiome emerged as a key controller of systemic immune homeostasis (Taur et al., 2020). It influences both local intestinal and systemic immune responses through intricate host–microbe interactions, shaping immune cell dynamics and maintaining mucosal tolerance while mediating protection from pathogens. (Schluter et al., 2020; Gopalakrishnan et al., 2018).

Substantial interindividual variations exist in microbial community structure and function, revealed by high-throughput sequencing and multi-omics approaches (Taur et al., 2020). Studies conducted on patients with hematopoietic cell transplantation have found that day-to-day variations in gut bacterial genera composition correlate with variations in neutrophils, lymphocytes, and monocytes. This indicates a direct relationship between gut microbiome structure and immune cell composition (Schluter et al., 2020). In cancer patients, gut microbiome diversity and composition have been consistently correlated with variations in antitumor immune response and treatment outcome (Gopalakrishnan et al., 2018; Jin et al., 2019).

Microbiome-immune crosstalk is defined as the bidirectional interaction between the host's immunity and its resident microbes (He et al., 2016). In other words, commensals regulate the host's immune tone, and alterations induced by immunity or treatment modify the resident microbes (Schluter et al., 2020; Stein-Thoeringer et al., 2023). With respect to lupus, gut microbiota alterations are correlated with imbalances in T helper cell subsets and inflammatory cytokines, thereby connecting dysbiosis with systemic immunity (He et al., 2016). In rheumatoid arthritis, alterations in microbial diversity have also been observed and are correlated with inflammatory markers and disease activity (Zhang et al., 2015). These evaluations collectively demonstrate that the components of the human microbiome regulate adaptive immunity polarization.

Systemic inflammation is a shared driver of multiple chronic diseases. In metabolic disorders, microbial dysbiosis correlates with chronic mild inflammation and impaired insulin sensitivity. In a large human cohort, reduced microbial diversity correlated with increased inflammatory mediators and metabolic dysfunction (Cotillard et al., 2013). Microbial translocation and endotoxin exposure are proposed contributors to this inflammatory state. Elevated circulating lipopolysaccharide levels have been linked to metabolic endotoxemia and chronic inflammation in human subjects (Caesar et al., 2015). These data indicate that the gut microbiota modulates systemic inflammatory tone. During intensive treatments such as chemotherapy and transplantation, antibiotic-driven microbiome disruption is associated with exaggerated inflammatory states, impaired immune reconstitution, and worse survival, illustrating how perturbation of gut-immune homeostasis can amplify systemic inflammatory damage (Schluter et al., 2020; Stein-Thoeringer et al., 2023).

The biology of cancer further underlines the role of inflammation. Landmark human studies of melanoma patients receiving anti-PD-1 (Programmed Death-1) therapy report that immunotherapy responders had unique gut microbiome signatures compared to non-responders. More diverse microbiomes and specific microbiome signatures correlated with better progression-free survival and systemic T cell response (Gopalakrishnan et al., 2018; Matson et al., 2018). This has been independently replicated, thereby solidifying the reproducibility of microbiome-immunotherapy relationships (Lee et al., 2022). Immune function analysis of these patients revealed enhanced antigen processing and positive CD8+ T cell responses in responders exhibiting favorable microbiome signatures.

Similarly, among patients with NSCLC, gut microbiome diversity and specific bacterial taxa correlated with clinical benefit from PD-1 inhibitor therapy (Jin et al., 2019; Hakozaki et al., 2020). In hepatoma, dynamic microbiome

changes during anti-PD-1 therapy were linked with treatment response and immune activation markers (Zheng et al., 2019). These results suggest that microbiome–immune interactions influence antitumor immunity across tumor types.

Throughout recent years, various human investigations have yielded direct evidence that the human microbiome influences immunotherapy responses. In melanoma patients, those responding to anti-PD1 immunotherapy had higher microbial diversity and increased Ruminococcaceae and *Faecalibacterium* in their microbiome; moreover, they had increased density of CD8+ T cells and enhanced systemic effector T cell responses (Gopalakrishnan et al., 2018). Additionally, interventional evidence has also enhanced the causal framework. In a clinical proof-of-concept trial, FMT from melanoma responders to anti-PD1-refractory patients yielded clinical responses in a proportion of these patients. Responsive patients had elevated activation of CD8+ T cells and modification of systemic immunologic pathways following FMT (Davar et al., 2021). This clinical study demonstrated that FMT can modify immunotherapy responses in human patients.

Microbial metabolites appear to be central to these interactions. In cohorts of patients with NSCLC and hepatocellular carcinoma, metabolomic analysis identified associations between SCFAs and augmented immune activation during ICI treatment (Wu et al., 2022; Sun et al., 2024). Nutritional components that regulate microbial metabolite production may also impact treatment outcomes. Increased dietary fiber intake has been correlated with augmented progression-free survival among melanoma patients undergoing ICI treatment, along with favorable microbiome composition. Conversely, over-the-counter probiotic supplements correlated with decreased microbial diversity and treatment response (Spencer et al., 2021).

Microbiota profile linked to immune-related toxicities. Certain intestinal microbiome signatures were linked to protection against ICI-induced colitis, whereas other signatures were linked to increased toxicity (McCulloch et al., 2022).

This review aims to integrate current knowledge of microbiome–immune crosstalk with particular emphasis placed on how microbiomes in the gut influence systemic levels of inflammation and how microbiomes can impact the efficacy of immunotherapy. This includes microbiome composition and function, immune signaling, and clinical implications in cancer and inflammatory diseases. This knowledge may help in the design of microbiome-based biomarkers and modulation of immunotherapy for individual patients.

Basic structure of gut Microbiota

The human alimentary canal is known to harbor a rich microbial population. It has been established that there are plenty of microorganisms residing in the human gut. Metagenomic studies show that microbes are critical for human physiology. It has been established through large population sequencing studies that the gut microbiome consists of various bacterial taxa, namely Firmicutes and Bacteroidetes. There is also a contribution from other bacterial groups such as Actinobacteria, Verrucomicrobia, and Proteobacteria (Falony et al., 2016; Almeida et al., 2019).

Human cohort investigations reported that microbial diversity is highly variable among humans. In a study involving in-depth metagenomic analysis of over a thousand adult humans, high interpersonal variability in species composition, gene abundance, and metabolic pathways was found (Zeevi et al., 2021). Similar high variability in human microbiota composition was found in genome-wide metagenomic association studies, which analyzed human genetics and microbiota composition in a human population (Qin et al., 2021). However, a functional human microbiome core has been found. This refers to microbial genes and functions that are shared among humans despite variability in microbial composition (Falony et al., 2016).

Culture-based and metagenomic methods have also been improved to increase our knowledge of the gut microbial community. A large human bacterial genome collection of microbes in the human gut revealed countless uncharacterized

species that were not previously known or had not been included in previous reference genomes (Almeida et al., 2019). Such discoveries are important in increasing our knowledge of microbes in the human gut and their evolutionary adaptation to this environment. Similarly, a HumGut genome collection of human gut prokaryotic microbes combined metagenomic data from multiple human cohorts to create a reference genome (Hiseni et al., 2021).

Aside from bacteria, there are other kingdoms of microorganisms that contribute significantly to the structure of the gut ecosystem. Recent studies from the Human Microbiome Project have shown that fungal microorganisms, which are collectively known as mycobiome, are another dimension of diversity in the gut ecosystem (Nash et al., 2017). Viral microorganisms, specifically bacteriophages, are also known to contribute to the ecology of microbes.

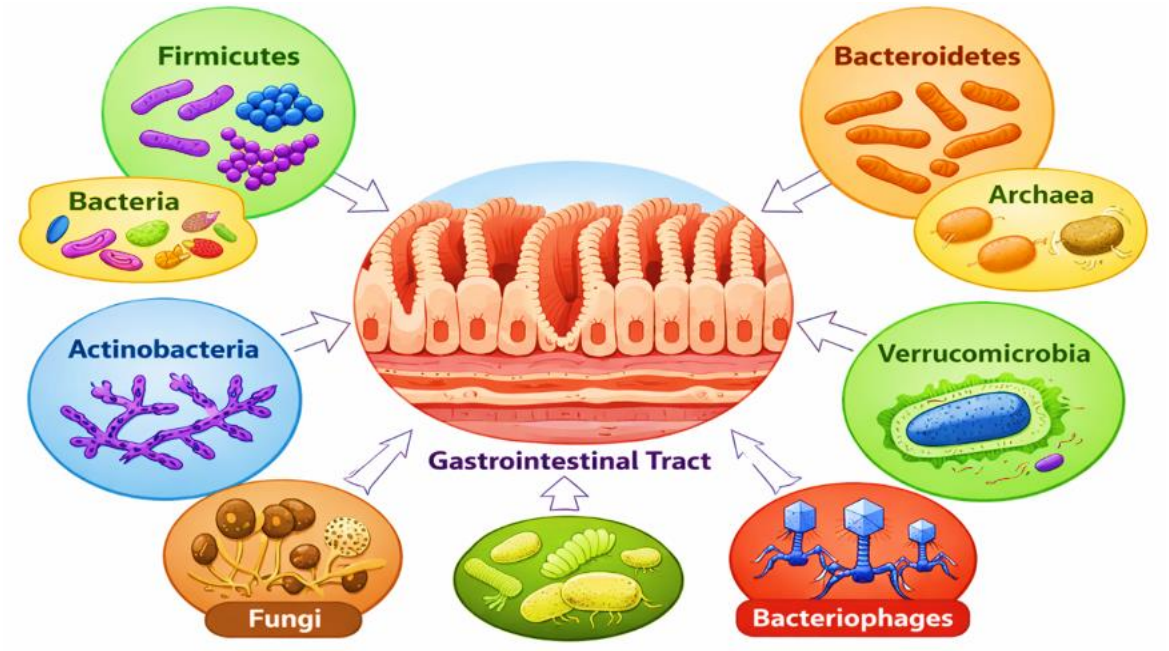

Figure 01: Structure and Composition of the Human Gut Microbiota

Factors shaping the microbiome

The structure of the gut flora is controlled by multiple host and environmental determinants. Diet is considered a major influence on the microbiome. Large-scale human cohort studies have shown that dietary patterns have a high correlation with microbiome diversity and gene richness in humans (Zeevi et al., 2021).

Another factor that affects the variation of the microbiome is the host's genetics. Genome-wide association studies on the microbiome's traits have shown host genetic loci associated with microbial abundance and microbial functions (Qin et al., 2021). This indicates that host-microbe interplay has some genetic components. However, the environment has more impact than the host's genetics.

Early life experiences are also shown to impact the development of the microbiome. Longitudinal studies on infants over the early months of life indicate that there are rapid changes in the microbial profile during early colonization (Hill et al., 2017). Delivery method, breastfeeding, and early antibiotic use are shown to impact the early life course of the microbiome.

Antibiotics and drugs also affect stability in microbiomes. Broad-spectrum antibiotics can reduce microbial diversity and eliminate beneficial commensal microbes. Resilience to such disturbances may require months or remain incomplete in certain individuals. Such effects usually result in a state of imbalance in microbes, referred to as dysbiosis. Eubiosis is a state of balance in a microbial population that maintains

homeostasis in a host. Dysbiosis refers to a disruption in a microbial population or its function. Dysbiosis usually results in reduced microbial diversity, increased opportunistic microbes, and altered metabolic activity. Human metagenomic research consistently associates dysbiosis with inflammatory and metabolic dysfunctions (Zeevi et al., 2021; Qin et al., 2021).

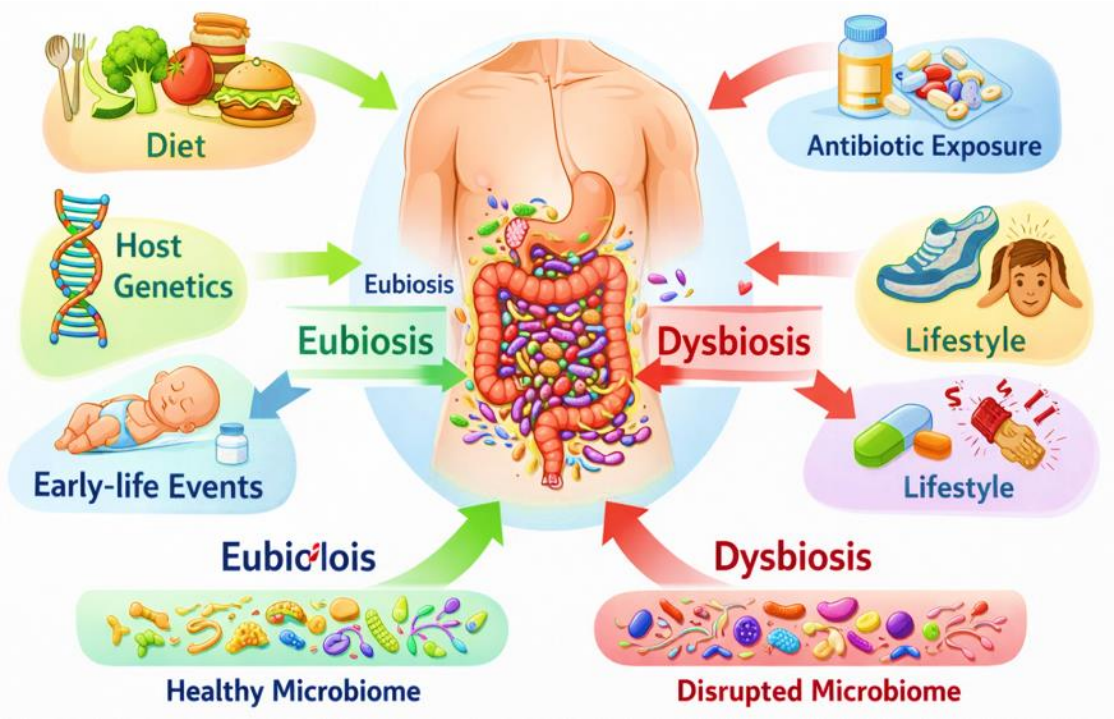

Figure 02: Key factors shaping gut microbiome composition

Functional roles relevant to immunity

Aside from taxonomic composition, there are various metabolic and immunological roles of the gut microbiome. Microbial metabolism has implications in the degradation of dietary compounds that are not completely broken down in the upper gastrointestinal system. The metagenome and metabolome have shown that microbes in the human gut are involved in carbohydrate metabolism, vitamin synthesis, and xenobiotic metabolism (Magnúsdóttir et al., 2019).

Among the most significant microbial compounds is the group of compounds termed SCFAs. These compounds, including propionate, acetate, and butyrate, are synthesized by the fermentation of dietary fiber by microbes. The production of SCFAs has been linked to human metabolomics and is related to specific microbial taxa and functional gene pathways (Zeevi et al., 2021). SCFAs have effects on barrier function, immune cell differentiation, and anti-inflammatory responses.

Microbial metabolisms also play a role in bile acid conversion. Bile acids fabricated by the liver are altered to secondary bile acids via microbial biotransformation. Bile acids participate in metabolic and immune pathways through host receptors. Human microbiome research has established a strong correlation between bile acid metabolisms and microbiota gene abundance (Magnúsdóttir et al., 2019).

Another significant functional pathway is microbial tryptophan metabolism. Microbes in the gut metabolize tryptophan from ingested food into indoles and other derivatives, which affect signaling pathways in the host. These indoles are known to affect barrier function in the intestine and immune cells. Active microbial genes in human gut microbiota, which are involved in tryptophan metabolism, have been found using

metatranscriptomic analysis (Schirmer et al., 2018).

Lastly, microbial metabolites have an impact on drug metabolism and response. Genomic functional analyses have shown that microbes have many enzyme-encoding genes that can alter pharmaceuticals and host compounds (Magnúsdóttir et al., 2019). The impact of microbes on drug response is evident in their ability to alter drug efficacy and availability.

These findings collectively illustrate that the human gut microbiome is an active metabolic system that intimately interacts with human biological systems. The taxonomic and functional diversity of this system is essential in regulating human metabolic processes, maintaining barriers, and controlling immunological signaling. The importance of this system composition and functionality is essential in elucidating microbiome-immune system interactions and their effects on systemic inflammation and immunotherapy.

Table 01: Key human studies linking gut microbiome composition to systemic immune responses

Study Design	Population	Key Microbial Findings	Immune Outcomes	Reference
Longitudinal cohort, metagenomics, and immune profiling	Hematopoietic cell transplantation patients	Microbial shifts track dominant bacterial genera.	Linked with circulating immune cell dynamics	Schluter et al., 2020
Multi-omics cohort with cytokine assays	Healthy adult volunteers	Taxa and pathways correlate with cytokines.	Predict host cytokine production capacity.	Schirmer et al., 2016
Population-scale microbiome association study	Large general population cohort	Diversity linked to environmental host factors	Correlates with inflammatory mediator levels	Zhernakova et al., 2016
Integrated multi-omics analysis	Human microbiome cohort	Functional microbial metabolic pathway variation	Associated with host immune gene expression	Heintz-Buschart et al., 2016
Longitudinal multi-omics cohort study	Inflammatory bowel disease (IBD) patients	Dysbiosis and altered microbial metabolism	Linked to mucosal immune dysregulation	Lloyd-Price et al., 2019
Clinical observational cohort	COVID-19 patients	Reduced beneficial taxa, opportunistic expansion	Correlates with inflammatory cytokine levels	Yeoh et al., 2021

Gut-associated immune system

The largest immune compartment is found in the gastrointestinal system. This is called the gut-associated lymphoid tissue. This encompasses Peyer's patches, mesenteric lymph nodes, and diffuse immune cells within the intestinal mucosa. These are always exposed to antigens found in the intestinal lumen. In humans, multi-omics studies report that the structure of the microbiota strongly impacts immune reactions (Schirmer et al., 2016; Lloyd-Price et al., 2019).

Population-level microbiome research also confirms that microbial diversity is linked to the presence of immune markers and immune mediators (Zhernakova et al., 2016; Heintz-Buschart et al., 2016). Innate immune responses are primary protection in intestinal mucosa. In this area of the host, there is a high density of macrophages, dendritic cells, neutrophils, and innate lymphoid cells of the lamina propria. These cells can sense microbes via pattern recognition receptors and quickly respond to a cytokine

signaling cascade. Cohort studies conducted in humans have revealed that changes in intestinal microbiota influence the cytokine production profile and innate immune activation pathway (Schirmer et al., 2016; Thaiss et al., 2016). An integrated metagenomics-based approach revealed that microbial metabolites are important in regulating inflammatory signaling and gene expression of leukocytes in the host (Heintz-Buschart et al., 2016; Lloyd-Price et al., 2019).

Adaptive immunity is also substantially impacted by microbial communities found in the gastrointestinal tract. T lymphocytes and Immunoglobulin A (IgA)-producing B lymphocytes are critical components of adaptive immunity in tissue from the gastrointestinal tract. Antigen stimulation by microbes is known to drive differentiation of regulatory T cells, which mediate tolerance to commensals. The human immunological profiling of microbial communities has found a positive correlation of microbial diversity with dynamics in lymphocytes (Schluter et al., 2020; Schirmer et al., 2016). Moreover, microbial composition is found to correlate with dynamics in lymphocytes and monocytes in longitudinal studies (Schluter et al., 2020; Zhernakova et al., 2016).

Microbial structural constituents may also be involved in systemic immunity. For instance, there is a large difference in the immunogenicity of various lipopolysaccharides of various bacteria found in the human gut. Longitudinal human studies carried out on children have established that structural components are pivotal in immune system ontogeny and the occurrence of autoimmune disorders (Vatanen et al., 2016). There is a vital role of variations in the immune stimulatory capacity of various microbes in individual variations in the inflammatory response and immune tolerance (Schirmer et al., 2016; Vatanen et al., 2016).

Clinical proof has also been provided to demonstrate that microbes can influence the immune response in disease processes. For example, there is a strong association that has been established regarding the microbiome and immune-related inflammatory disorders, namely IBD. For patients with IBD, studies demonstrate that modification in the microbiome can alter cytokine dysregulation and immune activation in the tissues of the patient (Hall et al., 2017; Lloyd-Price et al., 2019). Similar associations regarding microbiome and immune responses have been established in patient populations with colorectal cancer and correlations to inflammatory tumor microenvironments (Wirbel et al., 2019).

Latest human investigations have also proved that the intestinal microbiota regulates the body's immune response during an infection. In infected patients with COVID-19, the structure of the microbiota correlates with the proportion of inflammatory cytokines and the severity of the disease (Yeoh et al., 2021). This implies that the composition of the microbes can affect the body's antiviral immune response and the level of inflammation during an acute infection (Yeoh et al., 2021; Schirmer et al., 2016).

Moreover, the gut microbiota contributes to the control of therapeutic immune responses. Several clinical trials reveal that the microbial structure is a predictive factor of reception to immune checkpoint blockers in cancer therapy. Patients with high microbial diversity have shown improved response rates to anti-PD-1 immunotherapy (Gopalakrishnan et al., 2018; Matson et al., 2018). Similar studies were conducted in independent cohorts where bacterial species were found to increase anti-tumor immune activation (Routy et al., 2018; Dubin et al., 2016). Overall, human studies demonstrate that the gut microbiome critically modulates host immune function. This is because the gut microbiome is constantly in contact with the immune system of the intestine. This is known to affect cytokine production, immune tolerance, and systemic inflammatory responses. Notably, the gut microbiome can reorganize the immune response of other body systems. In this case, the immune system and microbiome interaction is essential for designing new approaches for immune modulation.

Mechanisms and Implications

The crosstalk between the gut microbiome and the immune system is regulated through various molecular mechanisms. The microbial metabolites

and structures, along with the immune signaling network, are some of the pathways that mediate the host-microbiome crosstalk. Cohort studies done among humans have shown that there is an effect of the gut microbiota on the immune system, as evidenced by functions of immune cells and levels of cytokines (Schirmer et al., 2016; Schluter et al., 2020).

Cohort investigations in humans have revealed that gut microbial diversity is linked to inflammatory mediators and immune phenotypes among individuals (Zhernakova et al., 2016; Kurilshikov et al., 2021). Studies done using omics approaches have shown that there is an effect of the interaction between microorganisms and the host on immune signaling pathways among individuals (Heintz-Buschart et al., 2016; Lloyd-Price et al., 2019).

This is because microbial metabolites represent major pathways of immune regulation. This is because the breakdown of dietary substrates through the process of fermentation is known to regulate the immune response. The human functional genomics studies have shown that microbial metabolic pathways are related to cytokine production in immune cells circulating in the human body (Schirmer et al., 2016; Zhernakova et al., 2016). The integrated approach of studying microbial and human metabolomes has shown that microbial metabolites are related to modifying human inflammatory pathways and immune response genes (Heintz-Buschart et al., 2016; Lloyd-Price et al., 2019). This demonstrates that microbial metabolites regulate immune response pathways in the human body (Schirmer et al., 2016; Kurilshikov et al., 2021).

Similarly, the role of the structural components of microorganisms has been found to be important for immune activation. The immunogenic potential of lipopolysaccharides has been found to be highly variable. The effects of the structural diversity of microorganisms in shaping the human immune system have been identified through studies conducted on humans (Vatanen et al., 2016; Schirmer et al., 2016). The input of the structural components of microorganisms has been identified to be crucial for the onset of autoimmune and chronic inflammatory disorders (Vatanen et al., 2016; Kurilshikov et al., 2021). The impacts of the structural diversity of microorganisms on the human immune system have been identified through microbiome studies.

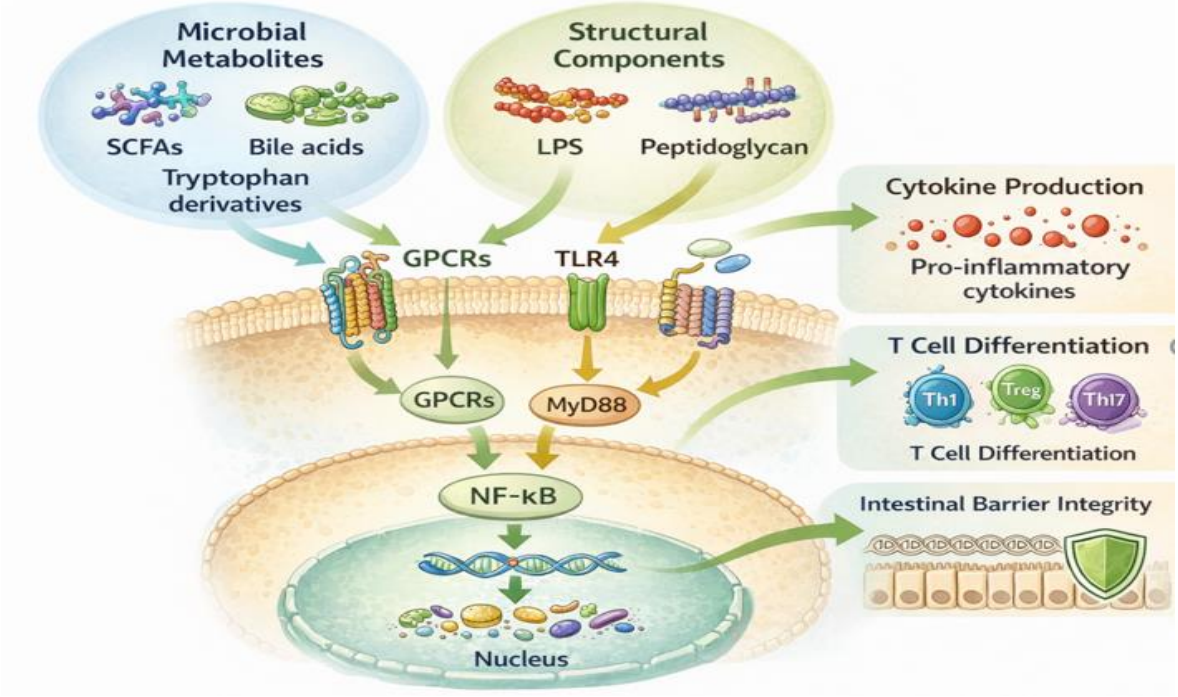

Figure 03: Molecular mechanisms of microbiome–immune crosstalk

Another significant mechanism is the modulation of differentiation in immune cells by microbes. Cohort studies carried out on human subjects indicate that variations in microbial structure in the gut are associated with immune cells, namely neutrophils and lymphocytes (Schluter et al., 2020). Such research has demonstrated that microbes are capable of regulating processes of hematopoiesis and immune regulation (Schluter et al., 2020; Kurilshikov et al., 2021). Furthermore, multi-omics studies were able to identify associations between microbial metabolic activity and processes of immune signaling in the host (Heintz-Buschart et al., 2016; Lloyd-Price et al., 2019).

Moreover, evidence of immune modulation by the microbiome during disease has been obtained. This has been exemplified by IBD, for which research indicates that the altered microbiome is associated with immune modulation, along with inflammatory pathways (Hall et al., 2017; Lloyd-Price et al., 2019). Moreover, the metagenomic meta-analysis of the microbiome of patients suffering from colorectal cancer has shown that the microbiome is linked to the inflammatory environment of the tumor (Wirbel et al., 2019). Similarly, the association of the microbiome with the immune response has been shown with respect to infectious diseases, for which dysbiosis influences the immune response (Yeoh et al., 2021).

Human clinical studies also prove that the microbiome indeed contributes to the therapeutic immune response. Various independent researches have proven that the structure of the microbiome can be used to forecast the success of immunotherapy for cancer treatment (Routy et al., 2018; Gopalakrishnan et al., 2018). Certain microbiome compositions are found to boost anti-tumor immunity for effective treatment outcomes (Matson et al., 2018; Routy et al., 2018). Certain studies have also proven that microbiome composition can be used to forecast negative impacts of immunotherapy (Dubin et al., 2016; Matson et al., 2018).

The function of microbiome and diet interaction may be related to immune crosstalk. Studies on humans have shown that the difference in glycemic response and the induction of metabolic-related inflammation are shaped by the microbial profile (Zeevi et al., 2015; Kurilshikov et al., 2021). Microbial metabolite production may integrate dietary inputs and immune response.

Overall, the evidence from human studies indicates that the human gut microbiome has a vital function to play in immune system modulation through various processes, including the regulation of immune cells, metabolites, structural elements, and metabolic pathways. However, the dysbiosis of the microbiome may disrupt these mechanisms, thereby contributing to inflammatory diseases.

Gut microbiota and systemic inflammation

Dysbiosis of gut microbiota is known to have adverse impacts on immunity and overall well-being. Antibiotics have adverse effects in that they kill healthy bacteria in the gut and can give rise to harmful bacteria. Cancers like cardiovascular diseases, rheumatoid arthritis, and obesity, which is associated with gut microbiota and is associated with various metabolic and gastrointestinal diseases, all relate to microbiota dysbiosis (Acevedo-Román et al., 2024). It is involved in various digestive disorders such as IBD, Irritable Bowel Syndrome (IBS), and *C. difficile* infections, and in systemic diseases, including obesity and neurological disorders. It leads to elevated levels of harmful substances and inflammatory mediators, causing damage to the gut and systemic inflammation and contributing to diseases like diabetes and Non-alcoholic Fatty Liver Disease (NAFLD) (Peña-Durán et al., 2025).

The gut microbiota is central to regulating systemic inflammation; dysbiosis may trigger a pro-inflammatory immune response. The loss of commensal microbes and the expansion of opportunistic pathogens raise levels of harmful substances like lipopolysaccharides (LPS) and pro-inflammatory cytokines, resulting in mucosal barrier damage and immune imbalance. This process heightens the risk for metabolic diseases, including diabetes, rheumatoid arthritis, and NAFLD, with obesity also associated with gut inflammation and microbiota imbalance (Zhao et al., 2023).

Dysbiosis of the gut microbiota is increasingly accepted as a leading factor of systemic low-grade inflammation. Immune activation and intestinal barrier failure are facilitated by changes in microbial diversity, pathobiont enrichment, and loss of beneficial commensals (Frankel et al., 2017). Patients with immune-mediated illnesses and cancer often exhibit diminished microbial diversity and shifts toward pro-inflammatory taxa like Bacteroidales and Enterobacteriaceae (Hanna et al., 2020).

Although the SCFAs synthesized by beneficial microbes induce anti-inflammatory responses and support gut barrier integrity, dysbiosis results in a pro-inflammatory response. LPS of Gram-negative bacteria enters the bloodstream through the compromised intestinal barrier. This activates TLR4 and NF-κB pathways. LPS also stimulates the production of pro-inflammatory cytokines, including TNF-α, IL-1β, and IFN-γ. This is termed as metabolic endotoxemia and is associated with type 2 diabetes, insulin resistance, obesity, NAFLD, IBD, and cardiovascular disease (Acevedo-Román et al., 2024; Peña-Durán et al., 2025; Zhao et al., 2023). Studies of IgA-deficient models show that there is increased intestinal permeability and high plasma endotoxin levels. This shows the importance of IgA in the control of microbial translocation and maintenance of mucosal homeostasis (Acevedo-Román et al., 2024; Peña-Durán et al., 2025).

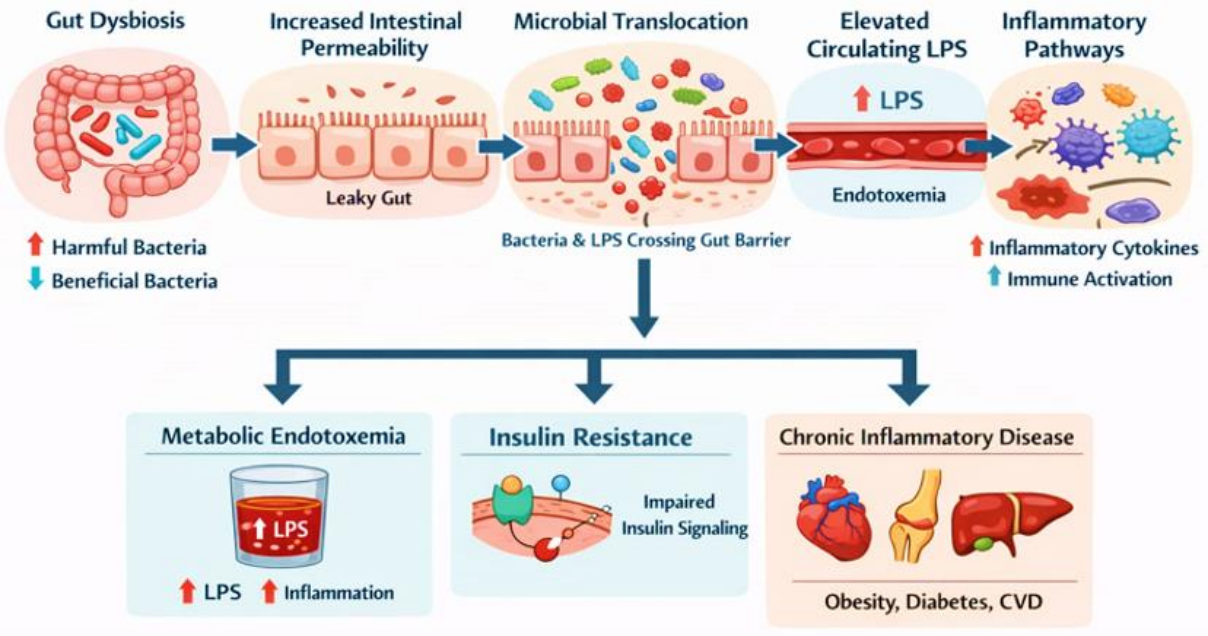

Figure 04: Gut dysbiosis and systemic inflammation

Increased systemic inflammation and tumor-associated immunological dysregulation are correlated with elevated circulating microbial products (Lee et al., 2022). By encouraging the maturation of regulatory T cells (Tregs), SCFAs generated by beneficial gut bacteria, namely Ruminococcaceae *and Faecalibacterium*, assist in retaining the integrity of the mucosal barrier and control immunological responses (Gopalakrishnan et al., 2018). When these taxa are lost during dysbiosis, less SCFA is produced, which increases intestinal permeability and stimulates the immune system (Zheng et al., 2019). Inflammatory and autoimmune illnesses are linked to changes in the microbiome. Multiple sclerosis, IBD, and rheumatoid arthritis can all be impacted by dysbiosis, which can cause uncontrolled immune activation through microbial antigens and cytokine imbalance (Frankel et al., 2017). Altered gut microbiota drives metabolic endotoxemia, insulin resistance, and adipose inflammation, making it an

important determinant in the advancement of metabolic diseases (Jin et al., 2019). Dysbiosis can promote cancer-associated inflammation, where microbial metabolites and inflammatory mediators alter the tumor milieu, affecting tumor growth and immune responses (Hanna et al., 2020). In individuals with metastatic melanoma, the commensal microbiota is linked to anti-PD-1 effectiveness (Matson et al., 2018).

The gut microbiome can help diagnose inflammatory disorders and predict treatment responses through microbial signatures (Lee et al., 2022). Certain gut microbes influence immunity. *Faecalibacterium prausnitzii* and Ruminococcaceae reduce inflammation, while Bacteroidales are linked to immunosuppression. (Gopalakrishnan et al., 2018). Additionally, circulating inflammatory mediators are indicators of immunological activation linked to the microbiota. Increased levels of endotoxins, microbial metabolites, and cytokines indicate inflammation brought on by dysbiosis and are associated with disease severity (Zheng et al., 2019). Microbial metabolites like bile acids, SCFAs, and tryptophan products regulate immunity and inflammation, serving as potential biomarkers of microbiome-immune interactions (Jin et al., 2019).

Table 2: Microbiome-based intervention strategies

Strategy	Mechanism of Action	Supporting Clinical Evidence	Effect on Inflammatory Biomarkers	Current Limitations	Reference
Dietary modification	Fiber-driven diversity; increased SCFA production	High-fiber diet linked to improved ICI response	↓C-Reactive Protein, Interleukin-6; improved immune tone	Adherence variability; heterogeneous responses	Spencer et al., 2021
Probiotics	Introduce beneficial live microbial strains.	Mixed clinical outcomes in cancer patients	Modest cytokine and immune modulation	Strain-specific effects; inconsistent colonization	Suez et al., 2019
Prebiotics	Substrates promote beneficial gut microbes.	Improved microbiota composition in trials	Increased SCFA; reduced inflammatory markers	Optimal dosing and duration unclear	Gibson et al., 2017
Synbiotics	Combined probiotic and prebiotic synergy	Early trials show microbiome restoration.	Improved SCFA profile; reduced inflammation	Limited oncology-specific clinical evidence	Swanson et al., 2020
FMT	Whole-community microbiome restoration	Restores PD-1 response in melanoma	↑$CD8^+$ T-cell activation; reduced suppressive cells	Donor variability; safety regulation concerns	Davar et al., 2021; Baruch et al., 2021

Microbiome Influence on Immunotherapy Effectiveness

Cancer immunotherapy boosts antitumor immunity by activating immune responses against cancer cells, primarily through ICIs that target PD-1, Programmed Death-Ligand 1 (PD-L1), and Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4). These treatments rejuvenate dysfunctional T-cells and boost antitumor immune responses (Chaput et al., 2017; Gopalakrishnan et al., 2018). Patients' clinical reactions to ICIs differ significantly from one another. Only a small percentage of patients get long-lasting tumor regression, suggesting that host-

related factors influence therapeutic effectiveness (Matson et al., 2018). Emerging data indicate that the gut microbiota shapes tumor microenvironment signaling and systemic immune responses, which in turn modulate immunotherapy outcomes (Peters et al., 2019).

Other immunotherapies that are beyond blocking checkpoint inhibitors include cell-based therapies like Chimeric Antigen Receptor T cell (CAR-T) cells and therapeutic vaccines, which require efficient antigen demonstration and stimulation of T cells (Frankel et al., 2017). Microbial composition may influence therapeutic strategies, as the microbiome regulates both adaptive and innate immune responses (McCulloch et al., 2022).

Table 03: Gut microbial taxa associated with ICI response across cancer types

Cancer Type	Therapy Used	Taxa Enriched in Responders	Taxa Enriched in Non-responders	Reference
Melanoma	Anti-PD-1 therapy	*Faecalibacterium*, Ruminococcaceae, Linsella, and high microbial diversity	Bacteroidales, reduced overall microbial diversity	Gopalakrishnan et al., 2018
Melanoma	Anti-PD-1 therapy	*Aerofaciens, Bifidobacterium longum, Col, and Enterococcus faecium*	Enrichment of *the Ruminococcus gnavus* group	Matson et al., 2018
Melanoma	CTLA-4 blockade (ipilimumab b)	*Faecalibacterium* and Firmicutes dominance	*Bacteroides*-dominant microbiome profile	Chaput et al., 2017
NSCLC / Renal cell carcinoma	PD-1/PD-L1 inhibitors	*Akkermansia muciniphila* enrichment, higher diversity	Reduced *Akkermansia*, antibiotic-associated dysbiosis	Routy et al., 2018
NSCLC	Anti-PD-1 therapy	Greater microbial diversity; high Firmicutes taxa	Reduced diversity; increased Proteobacteria	Jin et al., 2019
Hepatocellular carcinoma	Anti-PD-1 therapy	*Akkermansia*, Ruminococcaceae, SCFA-producing taxa	Increased Proteobacteria and opportunistic pathogens	Zheng et al., 2019

Clinical trials have proven that the microbiota of the human alimentary canal is critical to the effectiveness of checkpoint inhibitors. A clinical study in metastatic melanoma patients reported that respondents to anti-PD-1 treatment exhibited higher microbiota diversity, Ruminococcaceae, and *Faecalibacterium* than non-respondents. (Gopalakrishnan et al., 2018) Similar research found *Collinsella aerofaciens, Enterococcus faecium,* and *Bifidobacterium longum* to be concentrated in patients with favorable treatment outcomes. (Matson et al., 2018) In different cancer types, including renal cell carcinoma and NSCLC, patients responding to PD-1 treatment had higher *Akkermansia muciniphila*, leading to better progression-free survival. (Routy et al., 2018) When antibiotics are taken before immunotherapy, the response to treatment and survival are greatly reduced, proving the representation of microbiota in the effectiveness of treatment. (Derosa et al., 2018).

Additional research conducted in hepatocellular carcinoma and lung cancer revealed that certain signatures of microbes in the gut can differentiate responders from non-responders to anti-PD-1 treatment (Zheng et al., 2019). Similarly, certain

microbial pathways that are functional and are linked to activated immunity and progression-free survival in melanoma were revealed in a metagenomic-based study (Peters et al., 2019). Moreover, in recent times, microbiome-based therapies revealed causal therapeutic effects (Baruch et al., 2021). FMT from responders to immunotherapy can restore the ability to react to anti-PD-1 treatment and induce tumor regression among refractory melanoma patients (Davar et al., 2021). Such studies provide concrete evidence that the microbiome composition can impact immunotherapy outcomes.

Table 04: Clinical trials of FMT in cancer immunotherapy

Trial Phase	Patient Population	Donor Selection Criteria	Response Rate / Outcome	Immune Correlates	Reported Adverse Events	Reference
Phase II	PD-1–refractory metastatic melanoma (n=15)	Stool from prior ICI responders	~40% clinical benefit after FMT	↑$CD8^+$ T-cell activation; ↓ Interleukin-8 myeloid cells	Mostly mild gastrointestinal symptoms	Davar et al., 2021
Phase I	Anti-PD-1–refractory melanoma (n=10)	Donors with durable ICI responses	3/10 responses after FMT	Increased tumor immune infiltration signatures	No serious FMT-related toxicity	Baruch et al., 2021
Phase I	Advanced melanoma receiving PD-1 therapy (n=20)	Healthy screened microbiome donors	~65% objective response rate	Donor microbiome engraftment linked to response	Mostly immune-related ICI events	Baruch et al., 2023

Immunotherapy efficacy is modulated by gut bacteria through multiple molecular processes such as T cell stimulation and antigen processing (Routy et al., 2018). Certain commensal gut bacteria, for example, activate dendritic cells and enhance interleukin-12 production, causing tumor-specific $CD8^+$ T cell induction (Gopalakrishnan et al., 2018). Metabolites of these beneficial bacteria are also involved in immune priming. They increase immune surveillance and infiltration of effector lymphocytes into tumor sites (Frankel et al., 2017). Tumor infiltration of cytotoxic T cells and antigen-presenting cells is increased in responders, indicating that microbiota enhance immune signaling in cancer (Peters et al., 2019).

Beneficial gut microbes, which promote the secretion of inflammatory cytokines and inhibit the activity of T-regulatory cells and myeloid-derived suppressor cells, can, therefore, downregulate immunosuppressive signals in the tumor milieu, thereby enhancing tumor-suppressive immunity (Matson et al., 2018). These two processes, therefore, work together to produce a tumor microenvironment with an increased likelihood of being targeted by checkpoint blockade.

The therapeutic effectiveness and adverse effects of ICIs can be shaped by the gut microbiota (Chaput et al., 2017). Research in microbiome science reveals that particular signatures of gut microbiota are related to immune-mediated colitis in patients receiving immune checkpoint blockers (Dubin et al., 2016).

By identifying the microbial communities linked to toxicity during combination CTLA-4 and PD-1 blocking therapy, further recent studies have extended these results (McCulloch et al., 2022). Although some of the bacterial communities are found to be beneficial, others tend to enhance intestinal inflammation. These findings suggest that with the manipulation of the microbiome, the

profiling of the microbiome could be used to prevent immunotherapy-induced harm (Dubin et al., 2016).

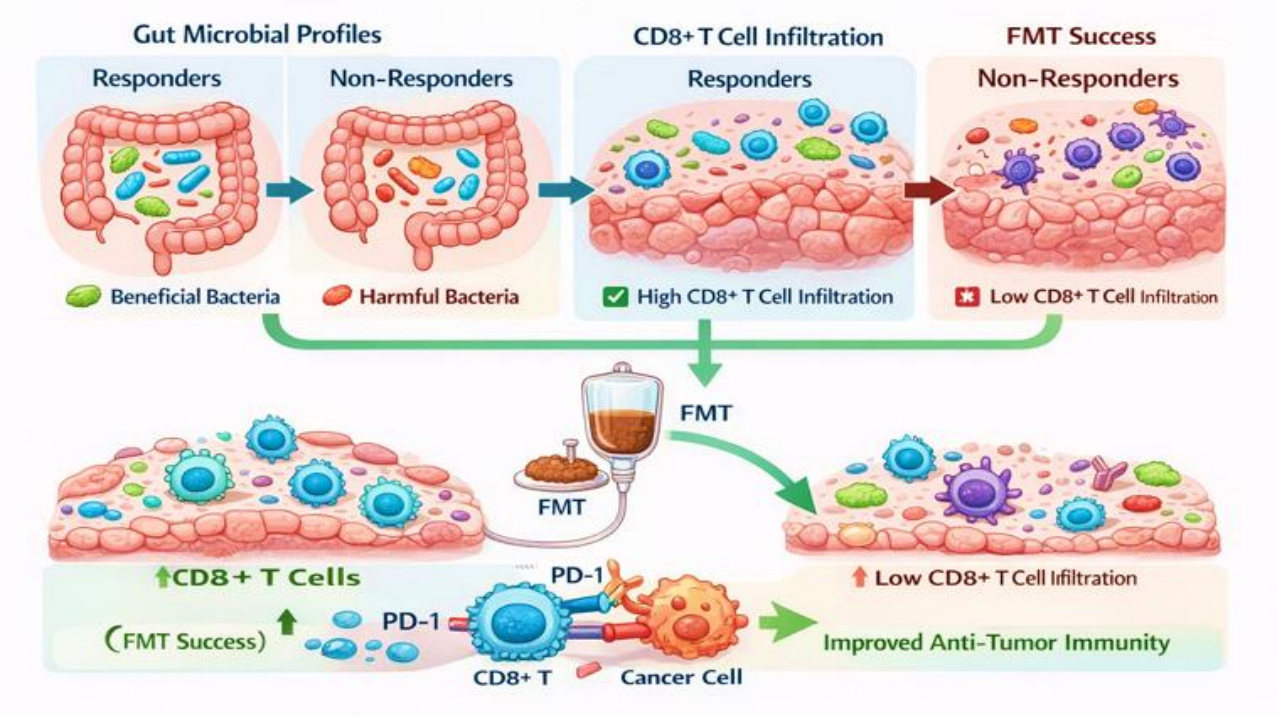

Figure 05: Microbiome–immunotherapy axis in cancer.

Strategies to Modulate the Microbiome for Better Immune Outcomes

Diet is considered one of the most influential regulators of the microbiome of the gut and is of critical significance with regard to immune response modulation. For instance, a high-bulk diet promotes microbial enrichment that has the ability to ferment complex carbohydrates to generate SCFAs, including butyrate, propionate, and acetate, thereby regulating immune homeostasis through discrimination of regulatory T-cells, intestinal barrier integrity, and anti-inflammatory effects (Shi et al., 2024).

High-fiber foods like whole grains, legumes, vegetables, and fruits are substrates for microbial fermentation and increase the diversity of the microbiome. Increased fiber intake has been associated with decreased inflammatory markers and improved metabolic outcomes, partly through microbial metabolite products (Harvard T.H. Chan School of Public Health, 2024).

Fermented foods are an alternative approach to microbiome modulation. A study of healthy adults found that, following a 10-week randomized dietary intervention, eating fermented foods like kefir, yogurt, kombucha, and kimchi increased microbiome diversity and decreased 19 inflammatory cytokines (Sonnenburg et al., 2021). Everyday routines, which include physical movements and psychological strain, also shape gut microbial structure. Regular physical activity is associated with enhanced microbial biodiversity and expansion of beneficial bacteria, which includes *Lactobacillus*, *Faecalibacterium prausnitzii*, *and Bifidobacterium*, which produce SCFAs and sustain intestinal barrier integrity. Exercise can modulate immune responses through several mechanisms, including strengthened gut barrier function, lowered systemic inflammation, and optimized metabolic regulation. However, excessive strenuous exercise may transiently elevate intestinal permeability and dysbiosis,

highlighting the importance of balanced training intensity (Hoseini et al., 2025).

Probiotics are viable microorganisms that provide therapeutic effects when given at appropriate doses. Common probiotic genera include *Bifidobacterium*, *Lactobacillus*, and *Saccharomyces*. These microbes modulate immune function via multiple mechanisms, including regulation of cytokine levels, strengthening of intestinal barrier integrity, and competitive inhibition of pathogens (Smolinska et al., 2025).

Synbiotics combine prebiotics and probiotics to improve microbial colonization and efficacy. In a study that utilized a randomized controlled trial design, synbiotic supplementation raised anti-inflammatory compounds, including interleukin 10 (IL-10) and secretory IgA, while lowering pro-inflammatory cytokines (Li et al., 2023).

A statistical analysis of 29 experimental studies comprising 1,633 participants demonstrated that probiotics, prebiotics, and synbiotics were associated with increases in beneficial microbial populations and inflammatory biomarkers, such as reduced levels of IL-1β and TNF-α (Zhang et al., 2025).

Recent investigations revealed that gut microbiota composition is important in determining the potency of immune checkpoint blockers in cancer treatment. In a clinical investigation involving a phase I trial of an association of FMT and PD-1 inhibitors in patients with metastatic melanoma, donor microbiota was successfully engrafted in patients, resulting in a 65 percent overall response rate (Baruch et al., 2023).

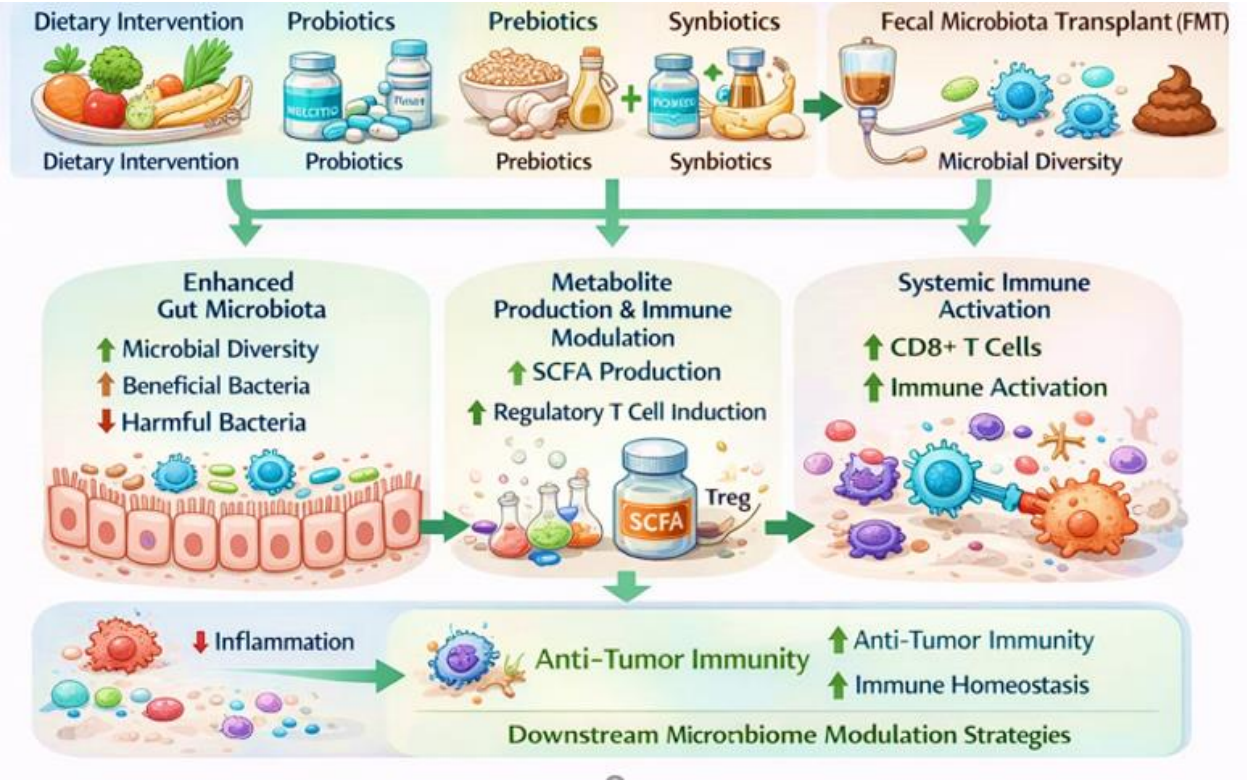

Figure 06: Microbiome modulation strategies and immune outcomes.

Challenges, Limitations, and Knowledge Gaps

Nevertheless, despite the rapidly expanding interest in microbiome-immune system interaction, there are still scientific and translational issues that are being encountered as barriers to the clinical application of microbiome-based immunotherapies. One of the major issues being encountered in the scientific investigation of the microbiome is the considerable inter-individual variability in microbial composition.

For example, host genetics, dietary patterns, age, geography, medication usage (such as antibiotics), and lifestyle are known to have considerable effects on microbiome diversity and function. Consequently, it is challenging to identify universal microbiome-based biomarkers, as they vary considerably between individuals and groups (Chen et al., 2024; Gilbert et al., 2025).

Furthermore, variability in sample collection and sequencing methods is also being encountered as another barrier to reproducibility (Gulyás et al., 2024). Another major knowledge gap is related to the difficulty of distinguishing causal relationships from associations in microbiome research. For instance, most human microbiome research is based on an observational study design, which is able to identify associations between microbiome components and health outcomes but is not able to establish whether or not microbiome components directly impact health or are a secondary response to physiological changes occurring in an individual (Islam et al., 2022).

Animal models, such as germ-free or antibiotic-treated mice, often serve as model systems for studying microbiome/immune interactions. Although such model systems offer valuable insights into microbiome/immune interactions, there is considerable divergence between human and mouse microbiomes. For instance, only a limited percentage of microbial genes are conserved across humans and mice, implying limitations in extrapolating animal model data to human clinical settings (Gopalakrishnan et al., 2019).

The lack of standardized methodologies is another major barrier in microbiome research. Sample collection methodologies, such as stool samples or mucosal biopsies, and DNA sequencing methodologies, such as 16S rRNA sequencing or shotgun metagenome sequencing, can greatly affect the microbiome profiles obtained from the same samples (Islam et al., 2022).

Similarly, safety and ethical issues have also emerged regarding microbiome-based therapeutic interventions, which include fecal microbiome transplantation, probiotics, and synthetic microbial communities. The transplantation of live microorganisms into patients can cause unforeseen ecological upsets in the host microbiome, which can eventually cause opportunistic infections, overgrowth of microorganisms, and dissemination of drug resistance (DeFilipp et al., 2019; Gulliver et al., 2022).

Table 05: Key challenges and knowledge gaps in microbiome–immune research

Challenge	Impact on Research	Proposed Solutions / Future Directions	Reference
Inter-individual microbiome variability	High variability limits reproducibility.	Personalized microbiome stratification approaches	Huttenhower et al., 2012
Causality vs. correlation limitations	Associations lack mechanistic confirmation.	Integrative multi-omics and controlled trials	Integrative Human Microbiome Project, 2019
Animal-to-human translation gaps	The murine microbiome differs from that of humans.	Humanized microbiome models, clinical validation	Nguyen et al., 2015
Methodological inconsistency	Sequencing and analysis pipeline variability	Standardized protocols and reporting guidelines	Knight et al., 2018
Safety concerns in microbiome therapies	Risk of pathogen transfer or dysbiosis	Strict donor screening and regulation	DeFilipp et al., 2019

Cases of bloodstream infections and sepsis, which resulted from poorly screened donor materials during FMT procedures, have also been documented, which further supports the need for strict screening of the donors. Moreover, the ethical issues associated with the use of microbial

therapy, such as informed consent, selection of the donors, and monitoring, need to be considered before its clinical use (Ejtahed et al., 2023; Gulliver et al., 2022).

Future Directions and Clinical Implications

A promising avenue for future research is microbiome-derived biomarkers to subtype patients before receiving immunotherapies. Multiple studies have demonstrated a positive correlation with reaction to ICIs when particular microbiome components are present. It is conceivable that by identifying such microbiome-based components, it may be possible to determine which patients would respond best to an immunotherapy, thereby increasing positive outcomes and reducing exposure to ineffective treatments (Liu et al., 2025).

Integration of microbiome information into various models of precision medicine may help in developing individual immunotherapy approaches. Personalized approaches may help in overcoming resistance to immunotherapy by re-establishing a favorable microbiome that promotes anti-tumor immune responses. (Chen et al., 2024)

Future research is also expected to increasingly involve integrated omics technologies, including metagenomics, metabolomics, transcriptomics, and immunomics, to obtain a thorough knowledge of microbe-host interactions. These integrated approaches are likely to help unravel the functional microbial pathways and products and immune signaling mechanisms that are involved in disease progression and treatment outcomes. Multi-omics data integration is also seen to hold promise for discovering new targets and biomarkers for disease treatment and prediction in microbiome-mediated diseases (Gilbert et al., 2025).

Conclusion

The gut microbiome is also a key modulator of immunity in the host. It governs the dynamics of immune cells and cytokine production and also regulates the inflammatory tone. Cohort studies, omics studies, and clinical trials indicate that the gut microbiome influences physiological and pathological outcomes. The balance is disrupted by dysbiosis. The loss of commensals, the increase of pathobionts, and the disruption of the barrier function of the intestine are responsible for chronic, low-grade inflammatory responses. This process is responsible for the pathogenesis of metabolic disorders, autoimmune diseases, and cancer-related immune disorders. A particularly promising avenue of association is that of the microbiome and cancer immunotherapy. Increased microbial diversity and certain microbes, such as *Faecalibacterium*, Ruminococcaceae, and *Akkermansia muciniphila*, are consistently linked to positive immunotherapy outcomes. Fecal microbiota transplant trials provide causal evidence of this association. Modulating the microbiome is a causal mechanism to re-establish immunotherapy effectiveness in non-responsive patients. Such evidence firmly establishes the microbiome as a malleable predictive factor of treatment outcome. Microbial metabolites are key players in this cross-talk. Bile acids, tryptophan metabolites, and SCFAs are important in regulating immune signaling, both locally and systemically. Diet, synbiotics, probiotics, and prebiotics are favorable directions to regulate these pathways in the context of immune function.

Significant challenges remain to be addressed. There are challenges of variability between individuals, inconsistency in methods, and challenges in establishing causality in human studies. Future studies should incorporate metagenomics, metabolomics, and immunomics to identify microbiome-based biomarkers that are reliable. This could open up avenues for developing personalized immunotherapy approaches to maximize the potential of microbiome-based interventions. The gut microbiome is a valuable focus for developing strategies to enhance immunity in a wide range of diseases.

REFERENCES

Acevedo-Román, A., Pagán-Zayas, N., Velázquez-Rivera, L. I., Torres-Ventura, A. C., & Godoy-Vitorino, F. (2024). Insights into gut dysbiosis: inflammatory diseases, obesity, and restoration approaches. International Journal of Molecular Sciences, 25(17), 9715.

Almeida, A., Mitchell, A. L., Boland, M., Forster, S. C., Gloor, G. B., Tarkowska, A., Lawley, T. D., & Finn, R. D. (2019). A new genomic blueprint of the human gut microbiota. *Nature Biotechnology, 37*(11), 1317–1326.

Baruch, E. N., Youngster, I., Ben-Betzalel, G., Ortenberg, R., Lahat, A., Katz, L., ... & Boursi, B. (2021). Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science, 371(6529), 602-609.

Baruch, E. N., Youngster, I., Ben-Betzalel, G., Ortenberg, R., Lahat, A., Katz, L., ... & Golan, T. (2023). Fecal microbiota transplantation combined with anti-PD-1 immunotherapy in advanced melanoma: A phase I trial. *Nature Medicine*.

Caesar, R., Tremaroli, V., Kovatcheva-Datchary, P., Cani, P. D., & Bäckhed, F. (2015). Crosstalk between gut microbiota and dietary lipids aggravates white adipose tissue inflammation through TLR signaling. *Cell Metabolism, 22*(4), 658–668.

Chang, J. W. C., Hsieh, J. J., Tsai, C. Y., Chiu, H. Y., Lin, Y. F., Wu, C. E., ... Chiu, C. H. (2024). Gut microbiota and clinical response to immune checkpoint inhibitor therapy in patients with advanced cancer. *Biomedical Journal, 47*(5), 100698.

Chaput, N., Lepage, P., Coutzac, C., Soularue, E., Le Roux, K., Monot, C., ... & Carbonnel, F. (2017). Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Annals of Oncology, 28(6), 1368-1379.

Chen, Y., Zhang, H., Li, M., & Wang, X. (2024). Modulating gut microbiome in cancer immunotherapy: Harnessing microbes to enhance treatment efficacy. *Journal of Translational Medicine, 22*(1), 1–14.

Cotillard, A., Kennedy, S. P., Kong, L. C., Prifti, E., Pons, N., Le Chatelier, E., ... Ehrlich, S. D. (2013). Dietary intervention impacts gut microbial gene richness. *Nature, 500*(7464), 585–588.

Davar, D., Dzutsev, A. K., McCulloch, J. A., Rodrigues, R. R., Chauvin, J. M., Morrison, R. M., ... Zarour, H. M. (2021). Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. *Science, 371*(6529), 595–602.

DeFilipp, Z., Bloom, P. P., Torres Soto, M., et al. (2019). Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplantation. *New England Journal of Medicine, 381*, 2043–2050.

Derosa, L., Hellmann, M. D., Spaziano, M., Halpenny, D., Fidelle, M., Rizvi, H., ... & Routy, B. (2018). Negative association of antibiotics on clinical activity of immune checkpoint inhibitors in patients with advanced renal cell and non-small-cell lung cancer. Annals of Oncology, 29(6), 1437-1444.

Dubin, K., Callahan, M. K., Ren, B., Khanin, R., Viale, A., Ling, L., ... & Wolchok, J. D. (2016). Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nature communications, 7(1), 10391.

Ejtahed, H. S., Parsa, M., & Larijani, B. (2023). Ethical challenges in conducting and the clinical application of human microbiome research. *Journal of Medical Ethics and History of Medicine*, 16, 5.

Falony, G., Joossens, M., Vieira-Silva, S., Wang, J., Darzi, Y., Faust, K., Kurilshikov, A., Bonder, M. J., Valles-Colomer, M., Vandeputte, D., Tito, R. Y., Chaffron, S., Rymenans, L., Verspecht, C., De Sutter, L., Lima-Mendez, G., D'hoe, K., Jonckheere, K., Homola, D., ... Raes, J. (2016). Population-level analysis of gut microbiome variation. *Science, 352*(6285), 560–564.

Frankel, A. E., Coughlin, L. A., Kim, J., Froehlich, T. W., Xie, Y., Frenkel, E. P., & Koh, A. Y. (2017). Metagenomic shotgun sequencing and unbiased metabolomic profiling identify specific human gut microbiota and metabolites associated with immune checkpoint therapy efficacy in melanoma patients. Neoplasia, 19(10), 848-855.

Gibson, G. R., Hutkins, R., Sanders, M. E., et al. (2017). The International Scientific Association for Probiotics and Prebiotics consensus statement on the definition and scope of prebiotics. *Nature Reviews Gastroenterology & Hepatology, 14*, 491–502.

Gilbert, J. A., Azad, M. B., Bäckhed, F., Blaser, M. J., Byndloss, M., Chiu, C. Y., ... & Knight, R. (2025). Clinical translation of microbiome research. *Nature medicine*, *31*(4), 1099-1113.

Gopalakrishnan, V., Helmink, B. A., Spencer, C. N., Reuben, A., & Wargo, J. A. (2019). The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy. *Cancer Cell, 33*(4), 570–580.

Gopalakrishnan, V., Spencer, C. N., Nezi, L., Reuben, A., Andrews, M. C., Karpinets, T. V., Prieto, P. A., Vicente, D., Hoffman, K., Wei, S. C., ... Wargo, J. A. (2018). Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. *Science, 359*(6371), 97–103.

Gulliver, E. L., Young, R. B., Chonwerawong, M., D'Adamo, G. L., Thomason, T., Widdop, J. T., ... Forster, S. C. (2022). Review article: the future of microbiome-based therapeutics. *Alimentary Pharmacology & Therapeutics*, 56(2), 192–208.

Gulyás, G., Kakuk, B., Dörmő, Á., Járay, T., Prazsák, I., Csabai, Z., Henkrich, M. M., Boldogkői, Z., & Tombácz, D. (2024). Cross-comparison of gut metagenomic profiling strategies. *Communications Biology, 7*, 1445.

Hakozaki, T., Richard, C., Elkrief, A., Hosomi, Y., Benlaifaoui, M., Mimpen, I., ... Routy, B. (2020). The gut microbiome associates with immune checkpoint inhibition outcomes in non-small cell lung cancer. *Cancer Immunology Research, 8*(10), 1243–1250.

Hall, A. B., Yassour, M., Sauk, J., Garner, A., Jiang, X., Arthur, T., ... Xavier, R. J. (2017). A novel *Ruminococcus gnavus* clade enriched in inflammatory bowel disease patients. Genome Medicine, 9, 103.

Hanna, D. L., Law, S. J., Merrick, S. A., Heptinstall, L., Bass, P., Dupont, P., & Sheri, A. (2020). The successful use of pembrolizumab in a renal transplant recipient with metastatic melanoma. Melanoma Research, 30(3), 321-324.

Harvard T.H. Chan School of Public Health. (2024). Fiber and fermented foods may aid microbiome and overall health.

He, Z., Shao, T., Li, H., Xie, Z., & Wen, C. (2016). Alterations of the gut microbiome in Chinese patients with systemic lupus erythematosus. *Gut Pathogens, 8*, 64.

Heintz-Buschart, A., May, P., Laczny, C. C., Lebrun, L. A., Bellora, C., Krishna, A., ... Wilmes, P. (2016). Integrated multi-omics of the human gut microbiome. Nature Microbiology, 2, 16180.

Hill, C. J., Lynch, D. B., Murphy, K., Ulaszewska, M., Jeffery, I. B., O'Shea, C. A., Watkins, C., Dempsey, E., Ross, R. P., Ryan, C. A., O'Toole, P. W., & Stanton, C. (2017). Evolution of gut microbiota composition from birth to 24 weeks in the INFANTMET cohort. *Microbiome, 5*, 4.

Hiseni, P., Karkman, A., Hultman, J., Bengtsson-Palme, J., & Larsson, D. G. J. (2021). HumGut: A comprehensive human gut prokaryotic genomes collection. *Microbiome, 9*, 204.

Hoseini, R., Rahim, H. A., Saifalddin, D. L., Kareem, D. A., & Fatah, A. M. (2025). Exercise intensity-mediated regulation of gut epithelial cells and immune function in gut microbiota dysbiosis. *Journal of Translational Medicine*, 24, 10.

Huttenhower, C., Gevers, D., Knight, R., Abubucker, S., Badger, J. H., Chinwalla, A. T., ... Human Microbiome Project Consortium. (2012). Structure, function and diversity of the healthy human microbiome. *Nature*, 486(7402), 207–214.

Integrative Human Microbiome Project Consortium. (2019). The integrative human microbiome project. *Nature, 569*, 641–648.

Islam, M. Z., Tran, M., Xu, T., Tierney, B. T., Patel, C., & Kostic, A. D. (2022). Reproducible and opposing gut microbiome signatures distinguish autoimmune diseases and cancers: A systematic review and meta-analysis. *Microbiome, 10*, 218.

Jin, Y., Dong, H., Xia, L., Yang, Y., Zhu, Y., Shen, Y., ... Lu, S. (2019). The diversity of gut microbiome is associated with favorable responses to anti-programmed death-1 immunotherapy in Chinese patients with non-small cell lung cancer. *Journal of Thoracic Oncology, 14*(8), 1378–1389.

Knight, R., Vrbanac, A., Taylor, B. C., et al. (2018). Best practices for analysing microbiomes. *Nature Biotechnology, 36*, 996–1004.

Kurilshikov, A., Medina-Gomez, C., Bacigalupe, R., Radjabzadeh, D., Wang, J., Demirkan, A., ... Zhernakova, A. (2021). Large-scale association analyses identify host factors influencing human gut microbiome composition. *Nature Genetics*, 53, 156–165.

Lee, K. A., Thomas, A. M., Bolte, L. A., Björk, J. R., de Ruijter, L. K., Armanini, F., ... Zhernakova, A. (2022). Cross-cohort gut microbiome associations with immune checkpoint inhibitor response in melanoma. *Nature Medicine, 28*(3), 535–544.

Li, X., Hu, S., Yin, J., Peng, X., King, L., Li, L., ... & Liu, L. (2023). Effect of synbiotic supplementation on immune parameters and gut microbiota in healthy adults: a double-blind randomized controlled trial. *Gut Microbes*, *15*(2), 2247025.

Liu, Q., Chen, Y., Zhang, Y., & Wang, L. (2025). The role of microbiome in immunotherapy: Insights and perspectives. *Seminars in Cancer Biology, 117*, 131–151.

Lloyd-Price, J., Arze, C., Ananthakrishnan, A. N., Schirmer, M., Avila-Pacheco, J., Poon, T. W..... Huttenhower, C. (2019). Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature*, 569, 655–662.

Magnúsdóttir, S., Heinken, A., Kutt, L., Ravcheev, D., Bauer, E., Noronha, A., Greenhalgh, K., Jäger, C., Baginska, J., Wilmes, P., Fleming, R. M. T., & Thiele, I. (2019). Generation of genome-scale metabolic reconstructions for 773 members of the human gut microbiota. *Nature Biotechnology, 35*, 81–89.

Matson, V., Fessler, J., Bao, R., Chongsuwat, T., Zha, Y., Alegre, M.-L., ... Gajewski, T. F. (2018). The commensal microbiome is associated with anti-PD-1 efficacy in melanoma. *Science, 359*(6371), 104–108.

McCulloch, J. A., Davar, D., Rodrigues, R. R., Badger, J. H., Fang, J. R., Cole, A. M., ... Zarour, H. M. (2022). Intestinal microbiota signatures of response and toxicity to anti-PD-1 therapy. *Nature Medicine, 28*(3), 545–556.

Nash, A. K., Auchtung, T. A., Wong, M. C., Smith, D. P., Gesell, J. R., Ross, M. C., Stewart, C. J., Metcalf, G. A., Muzny, D. M., Gibbs, R. A., Petrosino, J. F., & Highlander, S. K. (2017). The gut mycobiome of the Human Microbiome Project healthy cohort. *Microbiome, 5*, 153.

Nguyen, T. L. A., Vieira-Silva, S., Liston, A., & Raes, J. (2015). How informative is the mouse for human gut microbiota research? *Nature Reviews Microbiology, 13*, 1–14.

Peña-Durán, E., García-Galindo, J. J., López-Murillo, L. D., Huerta-Huerta, A., Balleza-Alejandri, L. R., Beltrán-Ramírez, A., ... & Suárez-Rico, D. O. (2025). Microbiota and inflammatory markers: a review of their interplay, clinical implications, and metabolic disorders. International journal of molecular sciences, 26(4), 1773.

Peters, B. A., Wilson, M., Moran, U., Pavlick, A., Izsak, A., Wechter, T., ... & Ahn, J. (2019). Relating the gut metagenome and metatranscriptome to immunotherapy responses in melanoma patients. Genome medicine, 11(1), 61.

Qin, N., Yang, F., Li, A., Prifti, E., Chen, Y., Shao, L., Guo, J., Le Chatelier, E., Yao, J., Wu, L., Zhou, J., Ni, S., Liu, L., Pons, N., Batto, J. M., Kennedy, S. P., Leonard, P., Yuan, C., Ding, W., ... Wang, J. (2021). Alterations of the human gut microbiome in liver cirrhosis. *Cell Discovery, 7*, 3.

Routy, B., Le Chatelier, E., Derosa, L., Duong, C. P., Alou, M. T., Daillère, R., ... & Zitvogel, L. (2018). Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. Science, 359(6371), 91-97.

Schirmer, M., Franzosa, E. A., Lloyd-Price, J., McIver, L. J., Schwager, R., Poon, T. W., Ananthakrishnan, A. N., Andrews, E., Barron, G., Lake, K., Prasad, M., Sauk, J., Stevens, B., Wilson, R. G., Braun, J., Denson, L. A., Kugathasan, S., McGovern, D. P. B., Vlamakis, H., ... Huttenhower, C. (2018). Dynamics of metatranscription in the inflammatory bowel disease gut microbiome. *Nature Microbiology, 3*, 337–346.

Schirmer, M., Smeekens, S. P., Vlamakis, H., Jaeger, M., Oosting, M., Franzosa, E. A., ... Xavier, R. J. (2016). Linking the human gut microbiome to inflammatory cytokine production capacity. *Cell*, 167, 1125–1136.

Schluter, J., Peled, J. U., Taylor, B. P., Markey, K. A., Smith, M., Taur, Y. ... Xavier, J. B. (2020). The gut microbiota is associated with immune cell dynamics in humans. *Nature, 588*(7837), 303–307.

Shi, J., Wang, Y., Cheng, L., Wang, J., & Raghavan, V. (2024). Gut microbiome modulation by probiotics, prebiotics, synbiotics and postbiotics: A strategy for disease prevention and treatment. *Critical Reviews in Food Science and Nutrition*.

Smolinska, S., Popescu, F. D., & Zemelka-Wiacek, M. (2025). Influence of prebiotics, probiotics, synbiotics, and postbiotics on the human gut microbiome and intestinal integrity. *Journal of Clinical Medicine*.

Sonnenburg, J. L., Gardner, C. D., et al. (2021). Fermented-food diet increases microbiome diversity and decreases inflammatory proteins. *Cell*.

Stein-Thoeringer, C. K., Saini, N. Y., Zamir, E., Blumenberg, V., Schubert, M.-L., Mor, U., ... Elinav, E. (2023). A non-antibiotic-disrupted gut microbiome is associated with clinical responses to CD19 CAR-T cell cancer immunotherapy. *Nature Medicine, 29*(4), 875–887.

Sun, L., Chen, G., Zhang, H., Liu, Y., Liu, C., Zhou, Q., ... Wang, J. (2024). Gut microbiota and metabolites associated with immunotherapy efficacy in small cell lung cancer. *Journal of Thoracic Disease, 16*(1), 45–58.

Swanson, K. S., Gibson, G. R., Hutkins, R., et al. (2020). The International Scientific Association for Probiotics and Prebiotics consensus statement on synbiotics**.** *Nature Reviews Gastroenterology & Hepatology, 17*, 687–701.

Taur, Y., Jenq, R. R., Perales, M. A., Littmann, E. R., Morjaria, S., Ling, L., ... Pamer, E. G. (2020). The effects of intestinal tract bacterial diversity on immune reconstitution following hematopoietic stem cell transplantation. *Nature, 577*(7790), 527–531.

Thaiss, C. A., Zeevi, D., Levy, M., Zilberman-Schapira, G., Suez, J., Tengeler, A. C. ... Elinav, E. (2016). Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell*, 159, 514–529.

Vatanen, T., Kostic, A. D., d'Hennezel, E., Siljander, H., Franzosa, E. A., Yassour, M., ... Xavier, R. J. (2016). Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. *Cell*, 165, 842–853.

Wirbel, J., Pyl, P. T., Kartal, E., Zych, K., Kashani, A., Milanese, A., ... Bork, P. (2019). Meta-analysis of fecal metagenomes reveals microbial signatures of colorectal cancer. *Nature Medicine*, 25, 679–689.

Wu, H., Zheng, X., Pan, T., Xu, Z., Zhao, C., Liu, Z., ... Zhang, J. (2022). Dynamic microbiome and metabolome changes during anti-PD-1 therapy in hepatocellular carcinoma. *International Journal of Cancer, 151*(9), 1409–1422.

Yeoh, Y. K., Zuo, T., Lui, G. C.-Y., Zhang, F., Liu, Q., Li, A. Y., ... Ng, S. C. (2021). Gut microbiota composition reflects disease severity in COVID-19 patients. *Gut*, 70, 698–706.

Zeevi, D., Korem, T., Zmora, N., Israeli, D., Rothschild, D., Weinberger, A., Ben-Yacov, O., Lador, D., Avnit-Sagi, T., Lotan-Pompan, M., Suez, J., Mahdi, J. A., Matot, E., Malka, G., Kosower, N., Rein, M., Zilberman-Schapira, G., Dohnalová, L., Pevsner-Fischer, M., ... Segal, E. (2021). Structural variation in the gut microbiome associates with host health. *Nature Medicine, 27*, 134–144.

Zeevi, D., Korem, T., Zmora, N., Israeli, D., Rothschild, D., Weinberger, A., ... Segal, E. (2015). Personalized nutrition by prediction of glycemic responses. *Cell*, 163, 1079–1094.

Zhang, X., Zhang, D., Jia, H., Feng, Q., Wang, D., Liang, D., ... Wang, J. (2015). The oral and gut microbiomes are perturbed in rheumatoid arthritis. *Nature Medicine, 21*(8), 895–905.

Zhang, Y., et al. (2025). Effects of probiotics, prebiotics, and synbiotics on gut microbiota and inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. *Nutrition Journal*.

Zhao, M. A., Chu, J., Feng, S., Guo, C., Xue, B., He, K., & Li, L. (2023). Immunological mechanisms of inflammatory diseases caused by gut microbiota dysbiosis: A review. Biomedicine & Pharmacotherapy, 164, 114985.

Zheng, Y., Wang, T., Tu, X., Huang, Y., Zhang, H., Tan, D. I., ... & Fang, W. (2019). Gut microbiome affects the response to anti-PD-1 immunotherapy in patients with hepatocellular carcinoma. Journal for immunotherapy of cancer, 7(1), 193.

Zhernakova, A., Kurilshikov, A., Bonder, M. J., Tigchelaar, E. F., Schirmer, M., Vatanen, T., ... Weersma, R. K. (2016). Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science*, 352, 565–569.