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(REVIEW ARTICLE)

The role of the gut microbiome in immune modulation: implications for autoimmune diseases and cancer therapy

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Abstract

The gut microbiome has emerged as a powerful regulator of immune function, profoundly influencing both autoimmune diseases and cancer therapies. Recent advances in microbiome research have unveiled the dynamic interplay between microbial communities and host immunity, revealing how microbial metabolites, bacterial surface molecules, and host-microbe interactions shape immune responses. This review explores the intricate mechanisms by which gut microbiota modulate immune tolerance, inflammation, and cancer immunosurveillance, highlighting the potential of microbiome-targeted interventions. Emerging therapeutic strategies, including fecal microbiota transplantation, engineered probiotics, and microbiome-derived metabolites, offer novel avenues for modulating immune dysfunction and enhancing treatment efficacy. Furthermore, artificial intelligence-driven microbiome profiling and CRISPR-based microbiome engineering hold promise for precision medicine, allowing personalized modulation of microbial ecosystems. Despite these breakthroughs, challenges such as interindividual microbiome variability, mechanistic gaps, and regulatory hurdles continue to impede clinical translation. Addressing these barriers will be crucial to unlocking the full potential of microbiome-based therapies in immune modulation, autoimmunity, and oncology. By integrating multi-omics approaches and advancing microbial therapeutics, the gut microbiome may soon transition from an adjunct to a cornerstone of precision medicine.

Keywords: Gut Microbiome; Immune Modulation; Autoimmune Diseases; Cancer Immunotherapy; Microbiota-Based Therapeutics; Precision Medicine; Fecal Microbiota Transplantation; Engineered Probiotics

1. Introduction

A vast and ever-changing population of bacteria known as the gut microbiome inhabits the human gastrointestinal system, which is increasingly acknowledged as a key factor influencing host physiology and general health. This highly diverse microbial ecosystem includes not only bacteria, which have been the primary focus of most early microbiome studies, but also a vast array of fungi (mycobiome), viruses (primarily bacteriophages), and archaea, many of which are yet to be fully characterized [1,2]. These microorganisms form a complex and symbiotic network that exists in a finely tuned balance with the host, engaging in both mutualistic and commensal interactions that influence virtually every

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aspect of gastrointestinal function and systemic biology. Far from being passive passengers, the members of the gut microbiota actively engage in digestion, vitamin synthesis, neurotransmitter production, and regulation of host immunity, among other vital roles [2].

Recent developments in the technique of high-throughput sequencing has greatly improved our comprehension of the richness, composition, and functional capacities of these microbial communities, especially in the areas of metagenomics, shotgun whole-genome sequencing and 16S rRNA gene sequencing [3]. These technologies have demonstrated the gut microbiome's taxonomic diversity as well as its potential applications in both health and illness. According to Lloyd-Price et al. [4], the intestinal barrier's integrity, host metabolic pathways, and the regulation of the immunological response are all impacted by the gut microbiota. Numerous clinical problems, including obesity, type 2 diabetes, neurological disorders, and inflammatory bowel disease, and even some types of cancer, have been linked to dysbiosis, or the dysregulation of this microbial community. As a result, there is a growing perception that the gut microbiota resembles an organ with the potential to have major systemic effects and to be a therapeutic aim in the management and prevention of several illnesses [4].

1.1. Overview of the Gut Microbiome

The gut microbiome is made up of trillions of bacteria that live in the human digestive system. The majority of these organisms are bacteria; the most prevalent phyla are Bacteroidetes and Firmicutes, which are followed by Verrucomicrobia, Proteobacteria, and Actinobacteria. According to the findings of Qin et al. [5], the microbiome of the human intestine has more than 3.3 million distinctive microbial genes significantly outnumbering the host's genetic material. In addition to bacteria, fungi (the mycobiome) such as *Candida albicans*, *Malassezia*, and *Saccharomyces boulardii* are integral to gut ecology, influencing immune responses and contributing to homeostasis or dysbiosis depending on their abundance and balance [6]. Viruses—especially bacteriophages—play crucial regulatory roles by modulating bacterial population dynamics through predation and horizontal gene transfer. The archaea in the human gut, although less abundant, are important in metabolic processes such as methanogenesis. Methanogenic archaea, particularly *Methanobrevibacter smithii*, are involved in breaking down complex carbohydrates and reducing hydrogen accumulation, thus influencing energy harvest and potentially contributing to obesity when dysregulated [7].

The gut microbiome exerts profound effects not only on local gut immunity but also on systemic physiological processes, including those of the central nervous system. As illustrated in Figure 1, the microbiota communicates with both the gut and the brain through a complex network of pathways involving the immune system, the vagus nerve, the neuroendocrine axis, the circulatory system, and the enteric nervous system [8,9].

The gut microbiome functions as a virtual organ as well, providing metabolic and immunological functions vital to host health. It participates in digesting dietary fibers, synthesizing vitamins like K and B12, regulating bile acids, and training the immune system during early life. Moreover, it forms a critical barrier against pathogen colonization by outcompeting invaders for nutrients and adhering to epithelial cells, a condition referred to as colonisation resistance [8]. Any alteration in its makeup, known as dysbiosis, has been connected to several diseases, including type-II-diabetes and obesity, autism spectrum disorder, inflammatory bowel disease (IBD), as well as diverse autoimmune diseases [9,10]. To better appreciate the diversity and immunological roles of gut microorganisms, Table 1 presents a summary of the major microbial taxa within the human gastrointestinal tract. It highlights representative species, their associated immune-modulatory metabolites, and the implications of their activity for health and disease.

Table 1 Major Microbial Taxa in the Human Gut and Their Immune Functions

Microbial Group	Representative Species	Immune Functions	Key Metabolites	Health Implications
Firmicutes	Clostridium spp. (clusters IV & XIVa), Faecalibacterium prausnitzii	Promote Treg differentiation, anti-inflammatory cytokine production	Butyrate, acetate	Enhances immune tolerance, reduces inflammation; decreased in IBD, RA
Bacteroidetes	Bacteroides fragilis	Induces Tregs, modulates dendritic cells and cytokine balance	Polysaccharide A (PSA)	Critical for immune balance; alteration linked to colitis and MS

Actinobacteria	Bifidobacterium longum, B. adolescentis	Enhance gut barrier integrity, stimulate IgA production	Lactic acid, acetate	Support mucosal immunity and tolerance; reduced in autoimmune diseases
Proteobacteria	Escherichia coli (AIEC strains), Klebsiella spp.	Activate pro-inflammatory pathways via TLRs	LPS (lipopolysaccharide)	Promote inflammation; enriched in IBD, RA, and CRC
Verrucomicrobia	Akkermansia muciniphila	Enhances epithelial integrity, modulates T cell responses	Mucin degradation products	Linked to improved response to immunotherapy (PD-1 blockade)
Archaea	Methanobrevibacter smithii	Supports SCFA-producing bacteria by reducing H2 accumulation	Methane	Associated with energy harvest and gut homeostasis; altered in obesity
Fungi (Mycobiome)	Candida albicans, Saccharomyces boulardii	Interact with immune cells, promote IL-17 production	β-glucans	Can support or exacerbate inflammation depending on balance
Viruses (Virome)	Bacteriophages (crAssphage, Siphoviridae)	Regulate bacterial populations, horizontal gene transfer	N/A	Influence microbiota stability and immune surveillance

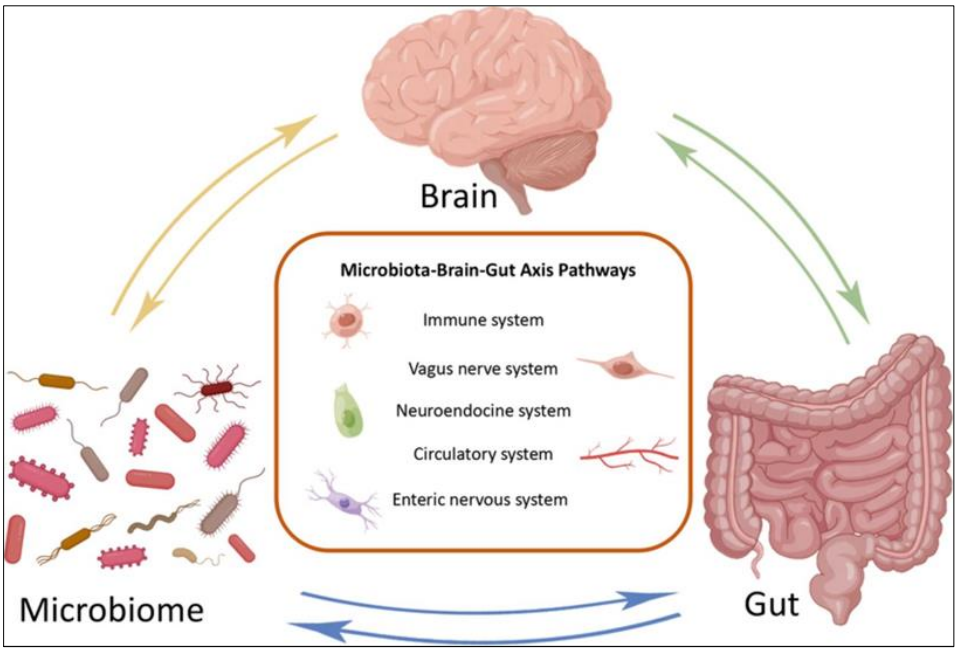

Figure 1 Bidirectional communication pathways in the Microbiota–Gut–Brain axis. Reproduced with permission from Ref. [10]

1.2. Gut Microbiota and the Immune System

Together with the human host, the gut microbiota has developed into a two-way regulatory axis with the immune system. An essential equilibrium between immunological tolerance and activation is established by the interaction, which starts at birth and lasts throughout life. The microbiota influences immunological responses that are both innate

and adaptive through various molecular and cellular mechanisms [11,12]. When commensal bacteria digest dietary fibres, short-chain fatty acids (SCFAs) such acetate, propionate, and butyrate are produced, which are among the gut microbiota's primary immune-modulatory products. From the findings of Furusawa et al. [13], SCFAs control the Foxp3 gene's epigenetic modification, this, in turn, controls the activity of regulatory T cells (Tregs), promoting tolerance and lowering inflammation. Additionally, it has been demonstrated that butyrate inhibits histone deacetylases (HDACs), which impact dendritic cells' and macrophages' cytokine expression [14].

Two pattern recognition receptors (PRRs) expressed on immune cells and gut lining epithelial cells are Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which make up another crucial interface. These receptors can recognise MAMPs, which include lipopolysaccharide (LPS), flagellin, and peptidoglycan. Nuclear factor-κB (NF-κB) and interferon regulatory factors (IRFs) are activated by TLR contact, which coordinate pro- or anti-inflammatory signalling pathways, according to Kusiak and Brady [15]. Immune homeostasis depends on the exact regulation of this signalling; unchecked activation can result in autoimmunity and chronic inflammation [15].

Furthermore, the gut microbiota influences antigen presentation, an essential part of the immune system's adaptation. Depending on the situation, the gut-associated lymphoid tissue's (GALT) dendritic cells send dendrites into the lumen to collect microbial antigens and transport them to CD4+ T cells using molecules of the major histocompatibility complex (MHC) class II, which directs their differentiation into Tregs or T-helper subsets [16,17]. It has been shown that certain bacterial taxa like Clostridium clusters IV and XIVa enhance Treg induction, which significantly affects the equilibrium between regulatory and effector T cells [18].

1.3. Objective and Scope of the Review

This review's main goal is to analyse the gut microbiota's immune-modulatory functions and clarify how It has an effect on the host immunological system to affect the course of cancer immunotherapy as well as autoimmune pathogenesis. Although homeostasis depends on the symbiotic relationship between immunity and microbiota, changes in microbial composition and metabolite production can lead to immune dysregulation, which is the root cause of autoimmune diseases such as systemic lupus, erythematosus rheumatoid arthritis, and multiple sclerosis. According to Zhang et al. [19], it has been possible to identify specific microbial signatures in patients with autoimmune diseases, suggesting a causative or exacerbating role of dysbiosis.

The gut microbiota's effects on cancer immunology will also be examined in this review, specifically as it relates to the efficacy of immunological checkpoint blockade treatments. Recent findings by Routy et al. [20] demonstrate that by promoting dendritic cell activity and T cell activation, some commensals, such as Akkermansia muciniphila, enhance the anti-PD-1 immunotherapy response in non-small cell lung cancer patients.

Additionally, we will go over new treatment techniques that aim to change the microbiome to enhance immunological control and clinical results. These consist of dietary changes, faecal microbiota transplantation (FMT), probiotics, prebiotics, and postbiotics. Microbiota-targeted immunomodulation has enormous potential as a new paradigm in disease prevention and therapy, especially as microbiome characterisation and personalised medicine become more widely available. With an emphasis on its translational potential for autoimmune and cancer treatment, This review attempts to provide a comprehensive and critical assessment of the gut microbiota – immune system interaction by synthesising existing evidence and outlining future prospects.

2. Gut Microbiota and Immune System Regulation

The immune system and gut microbiome have a link that is deeply intertwined, reflecting a long history of co-evolution between host and microbes. From early life, the gut's microbial colonization is essential in forming immune development, helping the body distinguish between harmless antigens and harmful pathogens. This intricate dialogue continues throughout life, with microbial signals continuously influencing immune homeostasis, tolerance, and activation. Disruptions in this balance have been increasingly associated with immune-related disorders, underscoring the importance of microbial communities in maintaining immune resilience. As research deepens, it becomes clear that understanding the gut microbiota's capacity to modulate the immune system is essential for understanding the fundamental mechanisms of health and disease [21,22].

2.1. Microbiota-Immune System Cross-Talk

Through complex mechanisms involving pattern recognition receptors, microbial metabolites, and cytokine signalling pathways, the gut microbiota is essential for controlling the immune system of the host. Short-chain fatty acids (SCFAs) are created when dietary fibre is fermented by proteobacteria. These SCFAs include butyrate, propionate and acetate.

Apart from supplying energy to colonocytes, these SCFAs have immunomodulatory effects via interacting with certain G-protein-coupled receptors (GPCRs) on immune cells. Regulatory T cell (Treg) development, which is essential for maintaining immunological tolerance and preventing excessive inflammatory reactions, might result from activation of these receptors [23].

Apart from SCFAs, the immune system is also impacted by the gut microbiota through the activation of toll-like receptors (TLRs), which are pattern recognition receptors that detect microbial-associated molecular patterns that aid the immune system in distinguishing between commensal and pathogenic microbes. Engagement of TLRs by microbial ligands triggers signalling cascades that produce cytokines and other mediators, which in turn shapes the immune response. For instance, TLR5 recognizes bacterial flagellin, and its activation has been connected to the control of gut microbial composition and intestinal homeostasis [24].

The dynamic relationship between gut microorganisms and the immune system is further demonstrated by cytokine signalling. The synthesis and operation of many cytokines, which are essential for immune cell communication and response regulation, can be influenced by microbial metabolites. This complex network of interactions underscores the importance of a balanced gut microbiota in sustaining immune equilibrium and highlights potential therapeutic avenues for managing immune-related disorders through microbiome modulation [24,25]. The gut's immune system maintains a delicate balance between tolerance and activation to ensure homeostasis. As shown in Figure 2, microbial metabolites and antigens interface with specialized intestinal cells, such as goblet cells and M cells, which in turn mediate immune responses via dendritic cell activation, cytokine secretion, and B and T cell modulation. This intricate dialogue contributes to the education of immune cells in structures like Peyer's patches and mesenteric lymph nodes, ultimately influencing systemic immunity and maintaining mucosal integrity.

To clarify how gut microorganisms influence immune responses, Table 2 outlines key microbiota-derived metabolites, their microbial origins, mechanisms of immune modulation, and implications for health and disease. These compounds represent promising targets for novel immunotherapies.

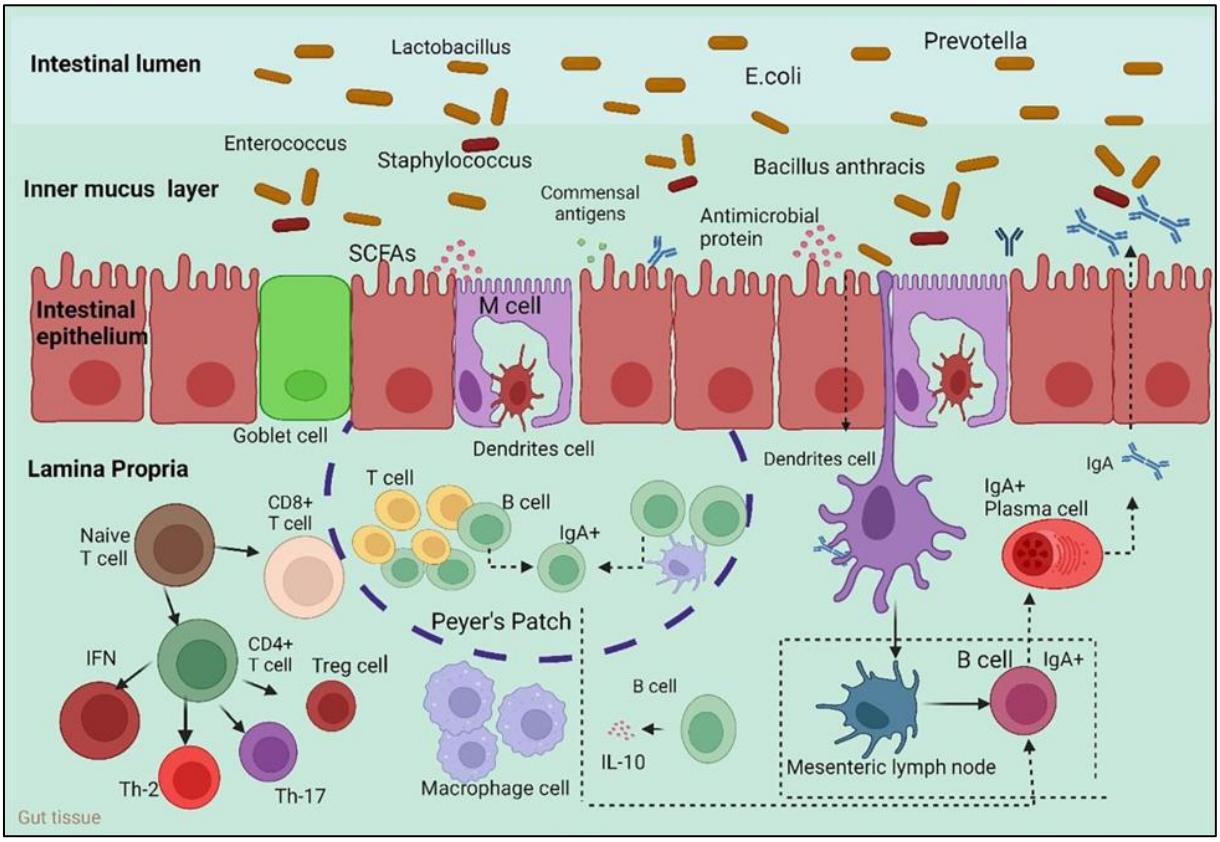

Figure 2 Schematic representation of gut microbiota-immune system interactions in the intestinal mucosa. Reproduced with permission from Ref. [25]

Table 2 Gut Microbiota-Derived Metabolites and Their Effects on the Immune System

Metabolite	Microbial Source(s)	Target Immune Pathways/Cells	Mechanism of Action	Health/Disease Relevance	Therapeutic Potential
Butyrate	Clostridium spp., Faecalibacterium prausnitzii	Regulatory T cells (Tregs), Dendritic cells	HDAC inhibition, Foxp3 gene epigenetic modulation	Anti-inflammatory, supports gut barrier; reduced in IBD, MS	Promotes Treg induction and mucosal healing
Acetate	Bifidobacterium spp., Akkermansia muciniphila	Neutrophils, Tregs	GPCR43 activation, mucin production	Maintains epithelial barrier, enhances Treg activity	Supports barrier integrity, modulates inflammation
Propionate	Bacteroides spp., Veillonella spp.	Tregs, Eosinophils	Histone acetylation, cytokine modulation	Regulates allergic responses and colonic inflammation	Modulates immune tolerance in allergic disease
Indole-3-lactate (ILA)	Lactobacillus spp.	Microglia, Tregs	AhR receptor activation	Reduces neuroinflammation, supports immune quiescence	Promotes remyelination in MS models
Polysaccharide A (PSA)	Bacteroides fragilis	Tregs, Dendritic cells	TLR2 engagement, IL-10 induction	Promotes immune tolerance, suppresses autoimmunity	Used in probiotic immunotherapy studies
Secondary Bile Acids	Clostridium spp., Bacteroides spp.	Macrophages, Dendritic cells	FXR and TGR5 signaling	Anti-inflammatory, controls NLRP3 inflammasome	Explored in IBD and metabolic disorders
Tryptophan Metabolites (e.g. Kynurenine, Indoles)	Bacteroides, Clostridium, Lactobacillus	Th17/Treg balance, Innate lymphoid cells	AhR and IDO pathway modulation	Influences mood, autoimmunity, gut-brain axis	Candidate for neuroimmune disorder modulation

2.2. Key Immune Cells Influenced by the Microbiome

The gut microbiota has a major impact on the development and function of many immune cells, forming a complex network of interactions that are necessary for preserving immunological homeostasis and combating infections. Among these immune cells, dendritic cells (DCs), T helper 17 cells (Th17), regulatory T cells (Tregs), and macrophages are particularly affected by microbial signals, which modulate their roles in antigen presentation, immune tolerance, inflammation, and innate immunity [27].

2.2.1. Dendritic Cells and Antigen Presentation

As the primary antigen-presenting cells that connect innate and adaptive immunity, dendritic cells are quite essential. They continuously sample the intestinal environment, capturing antigens from both commensal and pathogenic microorganisms. The gut microbiota significantly influences DC maturation and function through various microbial products. Toll-like receptors (TLRs) and other pattern recognition receptors on DCs are bound by peptidoglycans from bacterial cell walls and lipopolysaccharides (LPS) from Gram-negative bacteria, which causes these cells to mature and become active. Co-stimulatory molecules rise as a result of this activation, and cytokines that regulate T cell growth are released. On the other hand, DCs can have an anti-inflammatory phenotype due to microbial metabolites such as short-chain fatty acids (SCFAs), which encourage the conversion of naïve T cells into Tregs and support immunological tolerance in the gut environment [27,28].

2.2.2. Immune Tolerance and Regulatory T Cells (Tregs)

The production and function of regulatory T cells (Tregs) are significantly influenced by the gut microbiota. These Tregs which are necessary for immunological tolerance and limiting excessive inflammation. Certain commensal bacteria, particularly those belonging to the Clostridia class, have been demonstrated to encourage colonic Treg accumulation. This action is mostly mediated by SCFAs such as butyrate, which are formed during the fermentation of dietary fibre. By encouraging histone acetylation at the Foxp3 gene locus, which is necessary for Treg development, butyrate aids in the differentiation of naïve T cells into Tregs. Additionally, butyrate can activate G-protein-coupled receptors like GPR109a on DCs, leading to increased production of retinoic acid and further promoting Treg differentiation. These interactions underscore the importance of microbial metabolites in fostering intestinal environment with anti-inflammatory properties [29].

2.2.3. Th17 Cells and Inflammation Balance

One subset of CD4+ T cells that generates pro-inflammatory cytokines are T helper 17 cells. They are crucial for maintaining mucosal barriers and defending against extracellular infections. Th17 cell growth and activity are significantly regulated by the gut microbiome. Microbial-derived adenosine triphosphate (ATP) has been found to be a crucial element in encouraging Th17 cell differentiation. ATP released by commensal bacteria can activate lamina propria DCs via purinergic receptors, resulting in the generation of cytokines including IL-6 and IL-23, which are necessary for Th17 differentiation. However, an imbalance favoring Th17 cells over Tregs can contribute to inflammatory diseases, highlighting the necessity of a balanced microbial environment for immune homeostasis [30,31].

2.2.4. Macrophages and Innate Immune Activation

Macrophages are versatile innate immune cells involved in pathogen clearance, tissue remodeling, and the activation of inflammatory reactions. The gut microbiota influences macrophage polarization and activity through various microbial components and metabolites. LPS from Gram-negative bacteria can induce a pro-inflammatory M1 macrophage phenotype via TLR4 signaling, marked by the generation of cytokines such as IL-6 and TNF-α. In contrast, SCFAs, including propionate and butyrate, induce an anti-inflammatory M2 phenotype that is linked to tissue repair and inflammation resolution. The gut microbiota modulates macrophage activity, which is necessary to keep gut homeostasis stable and avoid chronic inflammatory diseases [27,32].

In general, by affecting the development and operation of vital immune cells, the gut microbiota significantly affects the immune system. Gut microorganisms contribute to the delicate balance of immunological activation and tolerance, which is critical for health and disease prevention, by producing different metabolites and interacting with immune receptors.

2.3. Impact of Dysbiosis on Immunity

Immunological equilibrium depends on the gut microbiota, a dynamic and diverse community of microorganisms found in the human gastrointestinal tract. A normal microbial ecology promotes optimal immune function, but changes to this balance—known as dysbiosis—can result in immunological malfunction, chronic inflammation, and increased vulnerability to numerous illnesses. The immunological consequences of dysbiosis also extend beyond local gut inflammation to systemic immune dysregulation. To better elucidate the link between dysbiotic states, immune mechanisms, and disease phenotypes, Table 3 presents a categorized overview of different types of dysbiosis, their mechanistic contributions to immune dysfunction, and the diseases with which they are commonly associated.

Table 3 Impact of Dysbiosis on Disease Pathogenesis

Type of Dysbiosis	Mechanism of Immune Disruption	Associated Disease(s)	Key Microbial Players	Relevant Metabolites / Molecules
Reduced microbial diversity	Loss of regulatory T cell induction, decreased SCFA production leading to impaired immune tolerance	Inflammatory Bowel Disease (IBD), Type 1 Diabetes, Multiple Sclerosis	Faecalibacterium prausnitzii, Bifidobacterium spp., Clostridium clusters IV/XIVa	Butyrate, acetate, propionate

Overgrowth of pathobionts	TLR overstimulation triggering excessive cytokine production and chronic inflammation	Rheumatoid Arthritis, Systemic Lupus Erythematosus, IBD	Escherichia coli (AIEC), Ruminococcus gnavus, Klebsiella spp.	LPS (lipopolysaccharide), flagellin
Loss of keystone commensals	Impaired gut barrier integrity, antigen leakage, systemic immune activation	Autoimmune diseases (MS, RA), Allergies	Akkermansia muciniphila, Bacteroides fragilis	Mucin-derived peptides, Polysaccharide A
Increased fungal and viral load	Activation of innate immunity via TLRs and inflammasomes, skewed Th17 responses	Ulcerative Colitis, SLE, Atopic Dermatitis	Candida albicans, Saccharomyces spp., crAssphage	β-glucans, dsDNA, TLR ligands
Early-life dysbiosis	Disrupted immune programming, reduced Treg formation, increased allergy risk	Asthma, Atopic Dermatitis, Type 1 Diabetes	Low Bifidobacterium spp., high Enterobacteriaceae	Imbalanced SCFAs, low indole derivatives

2.3.1. Dysbiosis and Immune Dysfunction

According to Sun et al. [33], dybiosis is defined by an imbalance in the microbial population, which frequently includes a decrease in helpful bacteria and an increase in harmful species. The intestinal barrier may be weakened by this imbalance, leading to increased permeability and what is frequently referred to as "leaky gut." Microbial substances like lipopolysaccharides (LPS) can enter the systemic circulation through the hole, causing an immunological response. Weiss and Hennet [34] found that this immune activation causes pro-inflammatory cytokines to be produced, contributing to systemic inflammation and immune dysregulation.

2.3.2. Chronic Inflammation and Disease Susceptibility

The pathophysiology of many illnesses has been linked to the chronic inflammation caused by dysbiosis. According to Shin et al. [35], abnormalities in the gut microbiota have been linked to gastrointestinal disorders including Crohn's disease and ulcerative colitis. IBD patients frequently have more pathogenic Proteobacteria and less commensal bacterial diversity. This microbial imbalance contributes to the chronic intestinal inflammation characteristic of these diseases.

Beyond the gut, dysbiosis has systemic implications. Atherly et al. [36] reported that changes in the makeup of the gut microbiota have been linked to metabolic diseases such as type 2 diabetes and obesity. Further connecting gut microbial composition to metabolic health, the inflammatory environment produced by dysbiosis might worsen insulin resistance and encourage inflammation of adipose tissue [36].

2.3.3. Microbiota and Mucosal Immunity

The mucosal immune system is largely educated and controlled by microbes in the stomach. As stated by Sun et al. [33], commensal bacteria engage in interactions with intestinal epithelial cells and immune cells to encourage the formation of regulatory mechanisms that stop unwarranted immune reactions. Dysbiosis can disrupt these interactions, resulting in a decline in immunological tolerance and a higher chance of developing autoimmune and allergy disorders. The relevance of microbial balance in immunological development is shown by the fact that, for example, a higher frequency of allergy disorders has been associated with less diversity in the gut microbiota throughout early life.

2.3.4. Therapeutic Consequences

Understanding how dysbiosis affects immunity has prompted research into microbiome-targeted treatments meant to improve immune-mediated illnesses and restore microbial balance. Weiss and Hennet [34] discussed that the promise of dietary interventions, probiotics, and prebiotics to modify the composition and activity of the gut microbiota is being investigated. Faecal microbiota transplantation (FMT) has been studied as a therapy option for recurrent Clostridium difficile infections, but research into its potential as a treatment for other dysbiosis-related disorders is currently ongoing.

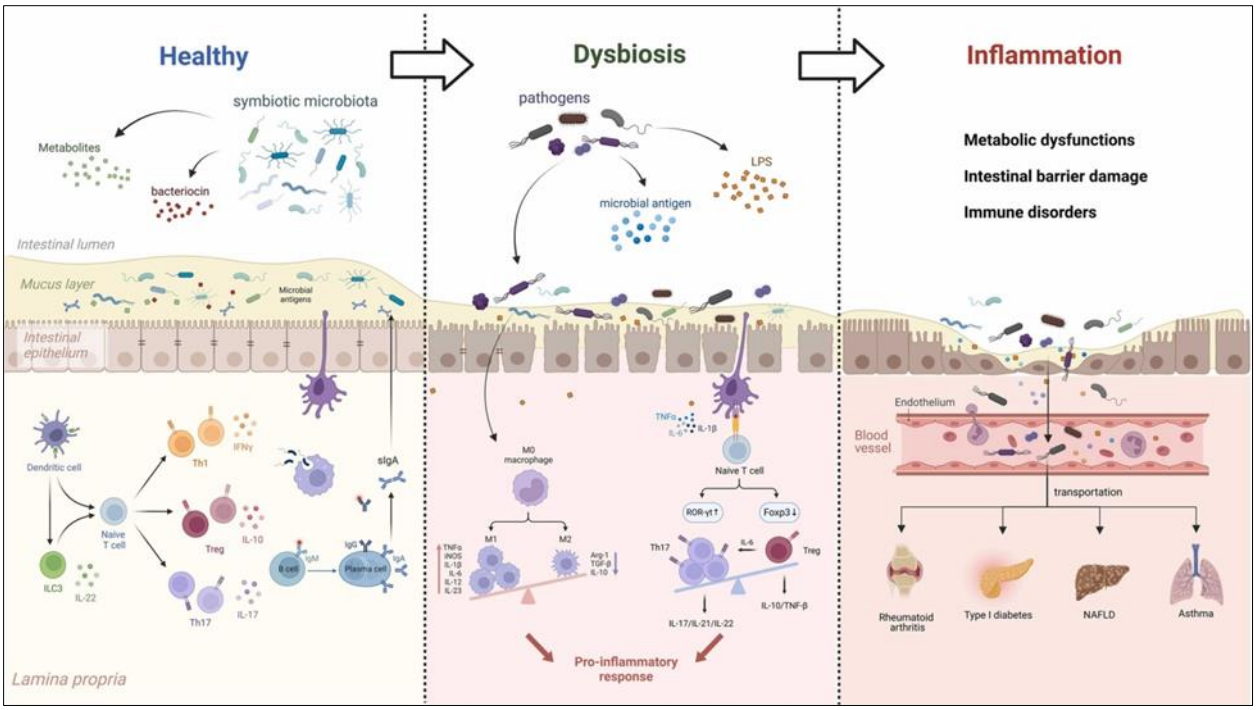

Figure 3 Gut Dysbiosis-Induced Immune Disruption and Systemic Inflammation. Reproduced with permission from Ref. [39]

3. Gut Microbiome and Autoimmune Diseases

The gut microbiome, a varied community of bacteria that inhabit the gastrointestinal system, is essential to immune homeostasis. Changes in this microbial ecology have been connected to a number of autoimmune illnesses, when the body's immune system mistakenly attacks its own tissues. Recent research has highlighted the intricate connections between gut microbes and the host's immune system, suggesting that modifications in the microbe composition may influence the onset and progression of conditions such as type 1 diabetes, systemic lupus erythematosus, and rheumatoid arthritis. Knowing these connections opens up exciting possibilities for new treatment approaches that modify the microbiota to re-establish immunological equilibrium [37].

3.1. The Role of Dysbiosis in Autoimmunity

Immune homeostasis and self-tolerance depend on the gut microbiota, a dynamic and diverse population of bacteria present in the human gastrointestinal tract. Numerous autoimmune illnesses have been related to dysbiosis, or abnormalities in the makeup and function of the gut microbiota. According to research by Christovich and Luo [38], dysbiosis can cause immune hyperactivation and a breakdown of self-tolerance, which may have a role in the development of autoimmune disorders.

3.1.1. Altered Gut Microbiota Composition and Immune Hyperactivation

According to Christovich and Luo [38], the immune system's proper development and function rely on a balanced gut flora. Commensal bacteria engage in interactions with immunological and intestinal epithelial cells, protecting self-tolerance and preventing autoimmune responses by promoting the growth of regulatory T cells (Tregs). Loss of self-tolerance and the onset of autoimmunity can result from disturbances in the gut microbiota that affect Treg differentiation and function.

Furthermore, pathogenic bacteria that create pro-inflammatory chemicals like lipopolysaccharides (LPS) can proliferate as a result of dysbiosis [39]. These compounds can activate the toll-like receptors (TLRs) on immune cells, which causes pro-inflammatory cytokines to be released and inflammatory pathways associated with autoimmune illnesses to be stimulated. Christovich and Luo [38] reported that it has been discovered that autoimmune disease patients have higher amounts of LPS, suggesting a link between dysbiosis, endotoxemia, and immune hyperactivation.

3.1.2. Intestinal Permeability and Autoimmune Pathogenesis

In order to stop infections and luminal antigens from moving into the systemic circulation, the intestinal barrier must remain intact. This barrier may be compromised by disturbances in the gut microbiota, which can result in increased intestinal permeability—a condition known as "leaky gut." According to research by Kinashi and Hase [40], a leaky gut permits food antigens and microbial products to enter the circulation, where they may cause systemic immune reactions and autoimmune disease development. Numerous autoimmune diseases, such as multiple sclerosis and type 1 diabetes, have been linked to increased intestinal permeability. Kinashi and Hase [40] observed that patients with these diseases often exhibit markers of compromised intestinal barrier function, pointing to a possible involvement of leaky gut in the aetiology of illness. Autoreactive immune cells may be activated as a result of microbial antigens moving into the systemic circulation, which would further encourage autoimmune reactions.

3.1.3. Mechanistic Insights into Dysbiosis-Induced Autoimmunity

Numerous theories have been put out to explain how intestinal permeability and dysbiosis fuel autoimmune. One such mechanism involves molecular mimicry, where microbial antigens resemble host tissues, causing autoreactive T cells to become activated. Suliman [41] discussed that certain gut bacteria possess antigens that mimic self-antigens, potentially triggering autoimmune responses through this mechanism. The change in the gut metabolome brought on by dysbiosis is another theory. The gut microbiota produces a variety of metabolites, including short-chain fatty acids (SCFAs), which have immunomodulatory effects. A reduction in SCFA-producing bacteria can lead to a decrease in these beneficial metabolites, resulting in impaired Treg function and increased inflammation. Haase et al. [42] highlighted that alterations in the gut metabolome can disrupt immune homeostasis and promote autoimmunity.

3.2. Microbiome and Specific Autoimmune Diseases

The connection between gut microbial dynamics and autoimmune disorders continues to reshape how these conditions are understood at the molecular and immunological levels. Each autoimmune disease appears to carry a distinct microbial signature, reflecting not just the loss of microbial diversity but also the expansion of potentially immunogenic species that influence disease onset and progression. Immunological dysregulation in several organ systems has been linked to alterations in the composition of the gut microbiota, suggesting that microbial alterations may play more than just a correlative role [43,44]. Rather than acting in isolation, these microbial patterns seem to interact intricately with host genetic susceptibility and environmental triggers to set the stage for disease pathogenesis. Unpacking the specific relationships between gut microbiota and particular autoimmune conditions reveals mechanistic insights that are shaping novel perspectives on both diagnosis and treatment [44].

Autoimmune diseases exhibit unique microbial imprints that contribute to immune dysregulation. To clarify the microbial patterns and underlying mechanisms across various conditions, Table 4 offers a comparative summary of gut microbiome alterations in key autoimmune diseases, highlighting their potential role in pathogenesis.

Table 4 Autoimmune Diseases and Microbial Alterations

Autoimmune Disease	Altered Microbial Species	Observed Dysbiosis Pattern	Proposed Mechanism	Key Immune Pathways Affected
Rheumatoid Arthritis (RA)	↑ Prevotella copri, ↓ Bifidobacterium and Clostridium spp.	Increased pro-inflammatory pathobionts, loss of SCFA producers	Molecular mimicry, Th17 polarization, TLR4 activation	IL-6, IL-17, TNF-α, Th17/Treg imbalance
Multiple Sclerosis (MS)	↓ SCFA-producing Clostridia, ↑ Akkermansia muciniphila, Methanobrevibacter	Reduced microbial diversity, disrupted SCFA metabolism	SCFA deficiency, altered microglial priming, Th17 overactivity	CNS inflammation, IL-23/IL-17 axis
Type 1 Diabetes (T1D)	↓ Bifidobacterium spp., ↑ Bacteroides dorei, Escherichia coli	Decreased microbial richness, impaired mucosal immunity	Reduced SCFA production, increased gut permeability	TLR4/NOD2 activation, autoreactive T cell stimulation

Systemic Lupus Erythematosus (SLE)	↑ Ruminococcus gnavus, ↓ Lactobacillus spp.	Expansion of pro-inflammatory taxa, reduced tolerogenic microbes	TLR2/TLR9 activation by bacterial DNA and lipoglycans	Type I interferon production, B cell hyperactivation
Inflammatory Bowel Disease (IBD)	↑ Escherichia coli (AIEC), ↓ Faecalibacterium prausnitzii	Loss of anti-inflammatory commensals, increase in Proteobacteria	Barrier dysfunction, chronic antigenic stimulation	IL-1β, IL-6, TNF-α, impaired Treg function

3.2.1. Rheumatoid Arthritis (RA)

In rheumatoid arthritis (RA), a chronic inflammatory illness, inflammation of the synovial joints results in pain, swelling, and perhaps joint destruction. With a focus on the bacteria *Prevotella copri* and the possible advantages of microbiome-based treatments, recent studies have illuminated the significant role that the gut microbiota plays in the pathophysiology of RA [45,46].

Role of Prevotella copri in RA Pathogenesis

Prevotella copri has been discovered to be significantly associated with the onset of RA. Approximately 75% of patients with newly diagnosed, untreated RA had greater P. copri abundances in their stool samples than healthy controls, according to a research by Scher et al. [47]. This overrepresentation suggests a potential link between *P. copri* colonization and the initiation of RA. The study also observed a corresponding reduction in beneficial gut bacteria, indicating that the proliferation of *P. copri* might disrupt the microbial balance, potentially contributing to systemic inflammation characteristic of RA. In similar study by Nii et al. [48], Thirteen strains of P. copri from RA patients' faeces (P. copri RA) were investigated to observe the potential role of Prevotella copri (P. copri) in rheumatoid arthritis (RA) by comparing said strains with healthy controls (P. copri HC). Significant genetic variety was found by genomic research, which also showed a region unique to P. copri RA that is linked to a conjugative transposon. Mice colonised with P. copri RA exhibited more severe arthritis than mice colonised with P. copri HC in arthritis models. Additionally, Bone marrow-derived dendritic cells were activated by P. copri RA to produce more IL-17 and Th17-related cytokines (IL-6, IL-23), suggesting a mechanism for its arthritis-inducing potential. These findings highlight the genetic diversity of P. copri and its possible involvement in RA pathogenesis.

The existence of P. copri in people at risk for RA has been investigated further. First-degree relatives of RA patients, a population thought to be at a higher risk of getting the condition, were studied by Alpizar-Rodriguez et al. [49]. Comparing pre-clinical RA patients to healthy controls, the results showed a substantial enrichment of P. copri in the former group. This suggests that alterations in the gut microbiota, namely the proliferation of P. copri, may take place before to and contribute to the start of RA.

Microbiome-Based Interventions

Since the gut microbiota has been linked to RA, treatment approaches that modify the microbiome have attracted attention. The potential of probiotic supplements to reduce RA symptoms has been studied. In a randomised, double-blind, placebo-controlled study, Zamani et al. [50] evaluated the effect of probiotics on inflammatory markers and clinical outcomes in RA patients. Participants receiving probiotic treatment showed lower levels of serum high-sensitivity C-reactive protein (hs-CRP) and Disease Activity Score-28 (DAS28), suggesting a reduction in inflammation and disease activity. The study concluded that probiotics might serve as beneficial adjunctive therapy in managing RA by modulating inflammatory responses [50,51].

Faecal microbiota transplantation (FMT), which involves giving patients faecal material from healthy donors in order to restore a balanced gut microbiome, is another strategy being considered. Although FMT has demonstrated potential in the treatment of some gastrointestinal conditions, its application in RA remains experimental. Preliminary studies suggest that FMT could potentially reestablish microbial equilibrium and alleviate autoimmune responses in RA patients. However, comprehensive clinical trials are necessary to assess the safety, efficacy, and long-term outcomes of FMT in the context of RA treatment [52,53].

Essentially, the connection between rheumatoid arthritis and Prevotella copri highlights the complex interplay between gut bacteria and autoimmune disorders. The growth of P. copri in RA patients and those at risk emphasises how gut dysbiosis may play a part in the aetiology of the illness. Probiotics and faecal microbiota transplantation are two

examples of microbiome-based therapies that provide promising paths for modifying the gut microbiota to slow the course and symptoms of RA. However, more thorough investigation is necessary to clarify the processes behind these correlations and provide efficient, focused treatments for RA [50-52].

3.2.2. Multiple Sclerosis (MS)

Multiple sclerosis (MS) is a chronic autoimmune illness in which the immune system attacks the central nervous system, resulting in demyelination and neurodegeneration. Emerging research indicates that gut microbiota may significantly influence MS pathogenesis, particularly concerning myelin degradation and neuroinflammation [54,55].

Influence of Gut Bacteria on Myelin Degradation and Neuroinflammation

According to a study published in *Neurology Neuroimmunology & Neuroinflammation*, individuals recently diagnosed with MS show notable variations in their gut microbiomes when compared to those in good health. The research identified specific gut bacteria with altered abundance in MS patients, suggesting a potential link between these microbial changes and the onset of MS [56].

More details are provided by a thorough investigation of the connection between gut microbiota and MS conducted by Ordoñez-Rodriguez et al. [57]. The study emphasises that although clinical data are still limited and equivocal, intestinal dysbiosis and changes in short-chain fatty acid-producing bacteria have been noted in MS patients.

3.2.3. Studies on Gut Microbiota Transfer Reducing MS Symptoms

Therapeutic strategies targeting the gut microbiome have been explored to alleviate MS symptoms. According to research presented by Larissa Jank, PhD, at the ACTRIMS Forum 2024 [58], supplementing animal models of multiple sclerosis with indole 3-lactate (ILA), a chemical generated by gut bacteria, may lessen the severity of the disease and encourage myelin repair. This finding indicates that modulating gut microbiota-derived metabolites may have therapeutic potential in MS [58].

Additionally, a study highlighted by *Multiple Sclerosis News Today* reports that ...the immune system's connections with gut flora are changed in MS, suggesting that restoring these interactions could be a potential therapeutic avenue [59]. Although these results are encouraging, more investigation is required to completely clarify the therapeutic potential of gut microbiota modification in multiple sclerosis.

In theory, the intricate relationship between gut flora and multiple sclerosis underscores the potential of microbiome-based treatments for MS. Myelin integrity and neuroinflammatory processes may be impacted by alterations in the composition of gut bacteria, which might accelerate the course of the disease. Promising approaches to lessening MS symptoms and encouraging brain healing include the use of bacterial metabolites like ILA and therapeutic approaches targeted at re-establishing a healthy gut microbiome. To test these strategies and provide efficient, focused therapies for MS, however, extensive clinical studies are necessary.

3.2.4. Type 1 Diabetes (T1D)

In type 1 diabetes (T1D), an autoimmune illness, the immune system destroys pancreatic β-cells, resulting in insulin insufficiency. According to new research, the pathophysiology of type 1 diabetes may be significantly influenced by alterations in the gut flora, especially in instances that develop early. These microbial changes can influence immune responses and impact pancreatic β-cell function through various metabolites [60,61].

Gut Microbial Alterations in Early-Onset T1D

Longitudinal cohort studies such as The Environmental Determinants of Diabetes in the Young (TEDDY) have improved our understanding of the role of the gut microbiota in the development of type 1 diabetes. Analysis of stool samples from newborns at genetic risk for T1D showed that those who had the condition had a decline in microbial diversity and stability in their early years of life (Vatanen et al., 2018). Specifically, decrease in microbes known for their immunomodulatory properties was observed, suggesting that such microbial imbalances may contribute to the autoimmune processes leading to β-cell destruction [62].

Paun et al. [63] provide more evidence for this by discussing the connection between pancreatic autoimmunity and disruptions in the gut microbiota. They emphasise how microbial metabolites might affect the immunopathology of T1D by controlling immune cells and β-cell activity in the pancreatic environment. These findings demonstrate how the composition of the gut microbiota may affect the onset and progression of disease [63].

Impact of Microbial Metabolites on Pancreatic β-Cell Function

Maintaining metabolic homeostasis and regulating host immunological responses depend heavily on the metabolites generated by the gut microbiota. Short-chain fatty acids (SCFAs), which are created when gut bacteria break down dietary fibres, are crucial for preserving the integrity of the intestinal barrier and have anti-inflammatory qualities, per a recent study by Blok et al. [64]. People with T1D have been demonstrated to lack SCFA-producing microorganism, which implies that lower amounts of these metabolites might be part of the inflammatory environment that promotes β-cell autoimmunity [64].

In experimental models, the administration of specific microbial metabolites has shown promise in modulating disease outcomes. Hill et al. [65] identified a protein produced by certain gut bacteria that stimulates the replication of insulin-producing β-cells. Their findings indicate that enhancing the presence of such beneficial microbes or their metabolites could offer novel therapeutic avenues for promoting β-cell regeneration and function in T1D [65].

According to the aforementioned, the relationship between the gut microbiota and immune system is intricate and important in the setting of T1D. Alterations in the gut microbial community may predispose people, especially in their early years, to autoimmune attacks on pancreatic β-cells. Microbial metabolites, such as SCFAs, are pivotal in maintaining immune balance and β-cell health. Understanding these relationships opens potential pathways for microbiome-targeted interventions aimed at preventing or mitigating T1D. To clarify the mechanisms at play and convert these discoveries into useful therapeutic treatments, more investigation is necessary.

3.2.5. Inflammatory Bowel Diseases (IBD) –Ulcerative Colitis and Crohn's Disease

Even though the precise cause of Inflammatory Bowel Diseases (IBD) is still unknown, a growing body of research suggests that an aberrant interaction between the host immune system and the intestinal microbiota plays a significant role in the onset and progression of these chronic immune-mediated conditions, which include ulcerative colitis and Crohn's disease. Alterations in microbial composition, coupled with impaired mucosal barrier function, have been closely linked to pathological immune activation, ultimately sustaining intestinal inflammation [66,67].

Disruptions in Gut Flora and Excessive Immune Activation

According to Frank et al. [68], a consistent feature across IBD cases is dysbiosis—a shift in microbial balance marked by a reduction in Firmicutes and Bacteroidetes and an expansion of Proteobacteria. These microbial changes not only affect nutrient metabolism and epithelial function but also promote aberrant immune responses. From the findings of Gevers et al. [69], Crohn's disease patients displayed a greater quantity of adherent-invasive *Escherichia coli* and decreased levels of anti-inflammatory *Faecalibacterium prausnitzii* in ileal biopsies. This imbalance correlated strongly with disease severity, suggesting a harmful function for some taxa of bacteria in driving intestinal immune dysregulation [69].

Pattern recognition receptors that are known to be activated by dysbiotic bacteria include nucleotide-binding oligomerisation domain-like receptors (NLRs) and toll-like receptors (TLRs). Mucosal damage is sustained because this molecular recognition triggers the downstream production of cytokines that promote inflammation, including IL-1β, IL-6, and TNF-α. According to Khor et al. [70], the exaggerated immune activation in IBD is also influenced by host genetic susceptibility, particularly polymorphisms in genes like NOD2 and IL23R, which modulate microbial sensing and immune signaling pathways. These genetic factors, in conjunction with microbiota alterations, create a pro-inflammatory environment that promotes chronic intestinal damage.

A Potential Treatment: Fecal Microbiota Transplantation (FMT)

Restoring microbial homeostasis has drawn a lot of attention as a means of reducing inflammation and re-establishing immunological tolerance in IBD. Faecal microbiota transplantation (FMT) is the process of transferring faecal matter from a healthy donor to a patient's gastrointestinal tract. A multicenter randomised experiment by Paramsothy et al. [71] revealed that patients with active ulcerative colitis who underwent rigorous FMT had noticeably greater rates of endoscopic improvement and clinical remission than the placebo group. The success of this intervention was closely associated with enriched beneficial taxa (such as *Lachnospiraceae* and *Ruminococcaceae*) and greater microbial diversity [71].

From the findings of Sokol et al. [72], responders to FMT exhibited a shift in mucosal immune cell populations, including a reduction in pro-inflammatory Th17 cells and increased presence of regulatory T cells, suggesting that the therapeutic benefit of FMT extends beyond compositional changes and involves direct modulation of immune responses. Furthermore, FMT trials in Crohn's disease have reported mixed outcomes, likely reflecting the disease's heterogeneity

and deeper transmural inflammation [72]. Despite these challenges, recent metagenomic studies have emphasized the potential of tailored microbial interventions that combine FMT with targeted dietary or prebiotic strategies to enhance therapeutic efficacy [72,73].

According to the aforementioned, ulcerative colitis and Crohn's disease are largely caused by disturbances in the gut flora by fostering maladaptive immune responses and impairing intestinal homeostasis. These alterations create a feedback loop of inflammation and microbial instability that perpetuates mucosal damage. FMT offers a compelling therapeutic avenue by reintroducing beneficial microbial populations capable of restoring immune regulation. Continued refinement of FMT protocols, coupled with deeper understanding of host-microbiome interactions, may help establish microbiota-centered approaches as mainstream treatments for IBD.

3.2.6. Systemic Lupus Erythematosus (SLE)

The generation of autoantibodies, persistent systemic inflammation, and multi-organ involvement—particularly affecting the kidneys, skin, and central nervous system— are characteristics of the complicated inflammatory disease known as Systemic Lupus Erythematosus (SLE). Growing evidence now backs a connection between gut microbial disturbances and the development and exacerbation of lupus pathology. Alterations in microbial taxa and exposure to microbial-derived molecules appear to contribute significantly to immune dysregulation in SLE, influencing both systemic autoimmunity and organ-specific manifestations such as lupus nephritis [74,75].

Increased Ruminococcus gnavus and Lupus Nephritis Correlation

According to Hevia et al. [76], SLE patients showed a large reduction in the variety of microbes and a notable rise in some pro-inflammatory taxa, with Ruminococcus gnavus being the most abundant of them. This increase was not random but showed a consistent association with disease flares and renal involvement. According to a detailed study by Lopez et al. [77], elevated levels of *Ruminococcus gnavus* were directly linked to the presence and severity of lupus nephritis. The bacterial strain's enrichment coincided with higher concentrations of anti-double-stranded DNA (anti-dsDNA) antibodies, major serological markers of lupus activity. The study further demonstrated that *R. gnavus* lipoglycans can stimulate plasmacytoid dendritic cells via Toll-like receptor 2 (TLR2), promoting the release of type I interferons— a class of cytokines that is essential to the pathophysiology of SLE [77].

Systemic immune responses seem to be impacted by this gut-resident bacteria in both direct and indirect ways. Increased bacterial component translocation and enhanced immune surveillance result from its growth, which is correlated with intestinal barrier failure. In SLE-prone mouse models, colonization with *R. gnavus* resulted in aggravated kidney inflammation, mimicking features of human lupus nephritis [78]. The recurring observation across animal and human studies suggests a mechanistic link between this bacterium and lupus-related renal pathology, potentially offering a microbial target for early risk stratification and intervention.

Role of Bacterial DNA in Lupus-Related Immune Dysfunction

Beyond microbial abundance shifts, the presence of extracellular bacterial DNA in circulation has also drawn significant interest in SLE research. According to Lood et al. [79], lupus patients displayed elevated levels of bacterial DNA in serum, often forming immune complexes with anti-DNA autoantibodies. These complexes activated plasmacytoid dendritic cells and promoted interferon-alpha secretion through TLR9 signaling, contributing to a self-sustaining loop of inflammation and autoantibody production. The inability of the immune system to differentiate between microbial DNA and host nuclear material appears central to this mechanism.

In experimental lupus models, bacterial DNA fragments derived from gut microbes were sufficient to induce anti-DNA antibody production and systemic inflammation, particularly when intestinal permeability was compromised. From the findings of Manfredo Vieira et al. [80], translocation of bacterial DNA into systemic circulation promoted the formation of immune complexes and accelerated glomerular damage in lupus-prone mice. This evidence reinforces the concept that not only bacterial cells but also their molecular signatures—such as DNA—can act as immunological triggers in genetically susceptible individuals [80].

In principle systemic Lupus Erythematosus is increasingly recognized as a disorder influenced by microbial-host interactions. The expansion of *Ruminococcus gnavus* in the gut and its link to lupus nephritis underscores the role of specific taxa in shaping autoimmune outcomes. In parallel, the systemic presence of bacterial DNA highlights the danger of molecular mimicry and uncontrolled immune activation. These findings all indicate that there may be novel approaches to the prevention and treatment of SLE, especially its renal symptoms, by focussing on the gut microbiome, either by microbial regulation or enhanced gut barrier integrity.

4. The Gut Microbiota and Immunotherapy for Cancer

The gut microbiota not only influences immunity in the local intestine but also plays a major role in systemic processes that regulate the progression of cancer and the efficacy of treatment. The substantial impact of gut microbiota composition on immune checkpoint inhibitor efficacy, adoptive cell treatments, and cancer vaccines has been brought to light by recent developments in cancer immunotherapy. Certain microbial communities enhance antitumor immunity by modulating antigen presentation, cytokine secretion, and T-cell activation, while dysbiosis can create an immunosuppressive environment that dampens therapeutic responses. Understanding the intricate connections between the immune system and gut microorganisms presents new chances to enhance immunotherapy tactics, enhance patient outcomes, and find biomarkers based on the microbiome for individualised cancer treatment.

4.1. The Microbiome's Function in Immune Evasion and Cancer Progression

The gut microbiota has a significant impact on both the immune system's response to tumours and the development of cancer. By interacting with the tumor microenvironment (TME), modulating immune checkpoint pathways, and affecting systemic inflammation, gut microbiota can either promote or inhibit tumor progression.

4.1.1. Influence on the Tumor Microenvironment, Immune Checkpoint Pathways, and Systemic Inflammation

The microbiota in the stomach affects the TME's many constituents, which include stromal elements, immune cells, and tumour cells, according to Liu et al. [81]. These microorganisms can modulate immune responses within the TME, affecting tumor growth and response to therapies [81,82]. From the findings of Li et al. [83], gut microbiota can influence immune checkpoint pathways, which are critical regulators of immune activation. By affecting these pathways, gut microbes can alter the effectiveness of immune responses against tumors.

Furthermore, gut microbiota can influence systemic inflammation by releasing various metabolites that enter the host circulation. These metabolites can modulate inflammatory cytokines, thereby impacting immune responses.

4.1.2. Microbial Metabolites in Cancer: Role of SCFAs, Polyamines, and Tryptophan Metabolites in Tumorigenesis

Tumorigenesis is significantly influenced by microbial metabolites, including polyamines, tryptophan derivatives, and short-chain fatty acids (SCFAs). Through a variety of processes, these metabolites can affect the genesis, development, and metastasis of cancer, according to Escriva et al. [84]. Dietary fibres ferment to create SCFAs, include propionate, acetate, and butyrate. These metabolites may lessen inflammation and carcinogenesis and have been demonstrated to alter immune responses [85]. Spermidine and spermine are examples of polyamines that are involved in the differentiation and proliferation of cells. Increased polyamine levels have been associated with the growth and dissemination of tumours. Indoles and other tryptophan metabolites have been associated with the formation of cancer cells and can affect immunological function. These metabolites have the ability to influence carcinogenesis and alter the immune system [86].

4.2. Gut Microbiome and Response to Cancer Immunotherapy

Patients differ greatly in the efficacy of immunotherapies for cancer, particularly immune checkpoint inhibitors (ICIs). According to new research, the gut microbiome's makeup significantly influences how the body reacts to various therapies. The effectiveness of immunotherapeutic treatments can be impacted by some bacterial species in the gut that disrupt the ability of the immune system to recognise and fight tumour cells [87]. Emerging evidence indicates that specific gut bacteria can modulate the success of immune checkpoint inhibitors. Table 5 outlines bacterial species associated with enhanced or diminished responses to cancer immunotherapy, highlighting their influence across different cancer types and treatment targets.

Table 5 Bacterial Species Linked to Immunotherapy Outcomes

Bacterial Species	Cancer Type	Immunotherapy Target	Clinical Effect	Proposed Mechanism of Action
Akkermansia muciniphila	NSCLC, Renal Cell Carcinoma	PD-1/PD-L1	Enhancement	Promotes dendritic cell recruitment and enhances CD4+ T cell infiltration into tumor beds

Faecalibacterium prausnitzii	Melanoma	PD-1	Enhancement	Produces SCFAs that enhance anti-inflammatory signaling and cytotoxic T cell responses
Bacteroides fragilis	Melanoma, Colorectal Cancer	CTLA-4	Enhancement	Stimulates Th1 responses and promotes dendritic cell maturation
Bifidobacterium longum	Melanoma (preclinical evidence)	PD-1	Enhancement	Boosts dendritic cell activity and supports CD8+ T cell priming
Enterococcus hirae	Lung, Kidney, Melanoma	PD-1	Enhancement	Enhances IL-12 production and cross-presentation of antigens via dendritic cells
Ruminococcus obeum	Melanoma	PD-1	Resistance	Linked with suppression of T cell function and promotion of immune escape pathways
Escherichia coli (pathogenic strains)	Pan-cancer	PD-1, CTLA-4	Resistance	Induces myeloid-derived suppressor cell expansion and systemic inflammation

4.2.1. Checkpoint Inhibitors (PD-1/PD-L1, CTLA-4)

Immunocheckpoint inhibitors that target programmed death-ligand 1 (PD-L1), programmed death-1 (PD-1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have revolutionized cancer treatment. However, the variability in patient responses has prompted investigations into underlying factors, including the gut microbiome's function [88].

Studies Linking Gut Microbiota Composition to Success or Failure of Checkpoint Blockade Therapies

According to Gopalakrishnan et al.'s research [89], melanoma patients who reacted to anti-PD-1 treatment had more diverse gut flora than those who did not. Specifically, responders had an increased abundance of *Faecalibacterium* and *Ruminococcaceae* species, which correlated with enhanced systemic and antitumor immune responses. In contrast, non-responders showed a predominance of *Bacteroidales*, associated with limited immune activation. These findings imply that positive reactions to checkpoint blockade treatments may depend on a varied and particular makeup of the gut microbiota [89].

Moreover, from the findings of Routy et al. [90] individuals undergoing anti-PD-L1 and anti-PD-1 therapy had better results when their gut microbiome contained specific bacterial species. Notably, improved clinical responses were linked to higher levels of Akkermansia muciniphila. There may be a way for the gut microbiome to increase checkpoint inhibitor efficacy, as patients with greater concentrations of this bacteria showed enhanced infiltration of CD4+ T cells into tumour beds.

Key Bacterial Species Enhancing Anti-PD-1 Efficacy

The ability of *Akkermansia muciniphila* to regulate immunological responses has drawn interest. According to Matson et al.'s research [91], individuals with melanoma who had *A. muciniphila* showed better responses to anti-PD-1 therapy. Mechanistically, this bacterium appears to enhance CD8+ T cell recruitment and activation in the tumour microenvironment, thereby potentiating antitumor immunity [91,92]. Although Bifidobacterium species have been linked to improving immune responses in preclinical models, it is unclear how they function in human research. Baruch et al. [93] state that the use of a multi-strain *Bifidobacterium* probiotic did not significantly alter outcomes in patients receiving checkpoint inhibitors. This suggests that the impact of *Bifidobacterium* on immunotherapy efficacy may be context-dependent and warrants further investigation.

These investigations highlight the intricate connection between gut bacteria and cancer treatment outcomes. It may be possible to increase the effectiveness of checkpoint blockade treatments by modifying the gut microbiota to encourage the development of beneficial bacterial species such as Akkermansia muciniphila. However, a more thorough comprehension of microbial interactions and how the immune system is affected by them is necessary to translate these results into therapeutic practice.

4.2.2. CAR-T Cell Therapy

Numerous host and environmental factors affect the effectiveness of chimeric antigen receptor T cell (CAR-T) therapy; in particular, the gut microbiota has recently attracted a lot of attention because of its ability to control systemic immunological preparedness [94]. Although CAR-T cell therapy is very effective in treating some haematologic cancers, faces challenges in solid tumors and in cases marked by treatment resistance or toxicity. There is increasing evidence that the gut microbiome influences toxicity, growth, and persistence of CAR-T cells in a controllable way. According to the findings of McPhedran et al. [95], germ-free or antibiotic-treated mice displayed diminished CAR-T cell efficacy, underscoring the importance of microbial-derived cues in sustaining T cell activation and memory. The study highlighted that microbial metabolites, particularly SCFAs like butyrate, promote CAR-T cell metabolism and enhance effector function by increasing histone acetylation at genes involved in cytotoxicity. Furthermore, from the findings of Stein-Thoeringer et al. [96], patients with a higher baseline abundance of Ruminococcaceae and Lachnospiraceae taxa exhibited improved outcomes following CD19-targeted CAR-T therapy. These bacterial groups appeared to regulate systemic inflammation and modulate cytokine release syndrome, a common and potentially fatal CAR-T-related toxicity.

Diet-based modulation and prebiotic supplementation are under exploration as strategies to prime the microbiome prior to CAR-T cell infusion. According to Mojgani et al. [97], patients receiving fiber-enriched diets before therapy demonstrated lower rates of cytokine storm and more favorable immune reconstitution post-treatment. This emerging connection between dietary intervention, microbial composition, and CAR-T outcomes emphasizes the microbiome as a key target in improving both safety and efficacy of next-generation immunotherapies [97].

4.2.3. Chemotherapy and Radiotherapy

Chemotherapy and radiation therapy, which are two therapies in the category of cytotoxic cancer therapies, have a major effect on healthy tissues, including the gut mucosa and its residing microbiota, as well as tumour cells. The host's reaction to these therapies can then be influenced by the integrity and makeup of the gut microbial population, especially through its effects on mucosal healing, systemic inflammation, and immunological reconstitution. According to the findings of Viaud et al. [98], certain commensal bacteria, such as *Barnesiella intestinihominis* and *Enterococcus hirae*, enhanced the efficacy of cyclophosphamide by stimulating Th17 and Th1 polarization. The depletion of these microbes in antibiotic-treated mice correlated with reduced therapeutic outcomes, highlighting the microbiome's role in supporting immunogenic cell death. Similarly, Iida et al. [99] demonstrated that antibiotic-induced dysbiosis impaired the recruitment of myeloid cells to tumors following platinum-based chemotherapy, ultimately diminishing anti-tumor immunity. These outcomes imply that maintaining microbiota diversity during chemotherapy is crucial to preserving immune priming.

In the context of radiotherapy, according to Gerassy-Vainberg et al. [100], radiation-induced intestinal injury was significantly exacerbated in mice with depleted commensals. Microbial loss led to increased intestinal permeability, bacterial translocation, and inflammatory cytokine release, compounding tissue damage. Moreover, the application of FMT (fecal microbiota transplantation) in irradiated mice accelerated mucosal repair and enhanced hematopoietic recovery, pointing to microbiota-based interventions as viable adjuncts to standard cancer therapies [100].

Altogether, these findings establish the microbiome not merely as a collateral target of cancer therapy but as a critical mediator of treatment efficacy and toxicity, with growing implications for patient-specific microbial profiling and supportive care strategies.

4.3. Microbiome-Based Strategies in Cancer Treatment

The complex connection between cancer treatment and the gut microbiota has led to research into microbiome-based approaches to improve patient outcomes and treatment effectiveness [101]. In order to increase anticancer immune responses and enhance treatment effectiveness, these strategies concentrate on modifying the gut microbiome.

4.3.1. Fecal Microbiota Transplantation (FMT) to Enhance Immunotherapy Response

In order to re-establish a balanced gut microbiome, patients undergoing faecal microbiota transplantation (FMT) receive faecal material from healthy donors. The potential of FMT to enhance responses to immune checkpoint inhibitors (ICIs) in cancer therapy has been examined in recent research. According to a National Cancer Institute study, patients with advanced melanoma who had not responded to ICIs showed excellent results after getting FMT from donors who had responded favourably to them. Specifically, six out of 15 patients exhibited either tumor reduction or disease stabilization post-FMT, suggesting that modifying the gut microbiome can influence immunotherapy outcomes [102].

Further supporting this, research by Liu et al. [103] indicates that FMT, when combined with immunotherapy, has shown promise across various cancer types. Larger clinical research is needed to confirm these findings and improve FMT techniques for cancer patients, the report highlights [103].

4.3.2. Probiotics and Engineered Bacteria to Boost Anticancer Immune Responses

The potential of probiotics—beneficial living microorganisms—to strengthen anticancer immunity has been investigated. According to a review by Marinelli et al. [104], specific probiotic strains can modulate the immune system, potentially improving responses to anticancer therapies [104]. Additionally, engineered bacteria are being developed to deliver therapeutic agents directly to tumors. Columbia University researchers have created probiotics that may safely deliver immunotherapies, such as nanobodies against CTLA-4 and PD-L1, into tumours. These engineered bacteria continuously release therapeutic agents, facilitating an immune response that results in tumor eradication [105].

Moreover, a study published in *Cell Reports Medicine* describes the development of an oncolytic and immunotherapeutic protein co-expressed by a multipurpose leaky probiotic. This engineered probiotic demonstrated enhanced anticancer immune responses and tumor eradication in preclinical models [103].

4.3.3. Dietary Modifications and Their Role in Therapy Outcomes

Dietary practices have a significant effect on the gut microbiome's function and composition, which in turn affects the results of cancer treatment. High-fiber diets have been associated with improved responses to immunotherapy. According to research funded by the National Institutes of Health, melanoma patients having a high-fiber diet intake had enhanced responses to ICIs in contrast to people who consume less fibre [106]. According to the study, dietary fibre may improve antitumor immunity by encouraging the development of beneficial gut flora.

Furthermore, research has shown that diets rich in polyphenols, such fruits and vegetables, positively alter the microbiome of the gut. An evaluation by Nguyen et al. [107] discusses how dietary components, including polyphenols, may affect the makeup of the gut microbiota and function, potentially impacting immune responses and cancer therapy outcomes.

All of these research highlight how microbiome-based strategies, including FMT, probiotics, engineered bacteria, and dietary changes, might boost anticancer immune responses can enhance the outcomes of cancer therapy. To create standardised procedures and completely clarify the mechanics behind these therapies, more study is necessary.

5. Emerging Microbiome-Based Therapeutics for Immune Disorders and Cancer

The therapeutic potential of the gut microbiome is no longer confined to theoretical frameworks; it is steadily shaping the contours of next-generation treatments for immune-mediated diseases and cancer. As mechanistic insights deepen, microbiome-targeted interventions are transitioning from experimental stages to clinical application [108]. This section explores the forefront of these innovations—ranging from precision microbial consortia and metabolite-based drugs to synthetic biology platforms—each offering a new dimension to immune modulation and oncologic therapy.

Advancements in microbiome research have paved the way for innovative therapeutic strategies targeting immune disorders and cancer. This section delves into emerging approaches, including next-generation probiotics, microbiome-derived metabolite therapy, CRISPR-based microbiome engineering, and personalized microbiome medicine, highlighting their potential in disease modulation and treatment optimization [108].

5.1. Next-Generation Probiotics and Live Biotherapeutics

Traditional probiotics have been recognized for their health benefits; however, recent developments focus on engineering microbial strains to enhance their therapeutic potential. These engineered probiotics, termed live biotherapeutics are intended to cure, prevent, or diagnose diseases by adjusting the host's defences [109]. Meng et al. [110] claim that because engineered probiotics have been genetically altered to target particular illnesses, treatments for inflammation, cancer, infections, and metabolic disorders have been created. To decrease systemic side effects and increase treatment effectiveness, several bacterial strains have been modified to carry anticancer drugs directly into tumour microenvironments [110–112].

Additionally, a review by Charbonneau et al. (2024) addresses how modified probiotics may be used to treat autoimmune illnesses, cancer, obesity, and inflammatory bowel disease. The authors point out that these living

biotherapeutics may be modified to generate certain proteins or metabolites that alter immune responses, providing a customised method of treating illness [109].

5.2. Microbiome-Derived Metabolite Therapy

The gut microbiota produces a variety of compounds that significantly affect host physiology and immunological function. Among them, tryptophan metabolites and SCFAs, or short-chain fatty acids, have garnered interest due to their potential to modulate illness [114]. According to research by Agus et al. [114], gut bacteria digest dietary fibres to produce SCFAs, including acetate, propionate, and butyrate. These metabolites may be used as treatment for illnesses such as colorectal cancer and inflammatory bowel disease because of their shown ability to control immunological responses, have anti-inflammatory properties and maintain the intestinal barrier's integrity.

Furthermore, the effects of tryptophan metabolites produced from the microbiome on health and illness are explained by Miyamoto et al. [115]. Serotonin and kynurenine, which are involved in immunological and mood control, are produced as a result of tryptophan metabolism. Numerous illnesses have been connected to disturbances in this metabolic system, suggesting that targeting tryptophan metabolites could offer novel therapeutic avenues [114,115].

5.3. CRISPR-Based Microbiome Engineering

The advent of CRISPR-Cas technology has revolutionised the field of genetic engineering by expanding its uses to the gut microbiota. This approach allows for precise editing of microbial genomes, enabling the modification of bacterial functions to influence host immunological reactions [116]. A thorough review by Abavisani et al. [116] claims that, utilizing the CRISPR-Cas system for microbiome editing holds promise for therapeutic interventions. The authors discuss how targeted gene editing can be employed to eliminate pathogenic bacteria or enhance the beneficial properties of commensal microbes, thereby modulating immune responses and potentially treating various diseases [116].

Moreover, research highlighted by Nath et al. [117] shows how phage-delivered CRISPR systems may be used to fight off infections that are resistant to drugs. This strategy involves using bacteriophages to deliver CRISPR-Cas components to specific bacterial populations, achieving targeted bacterial depletion without disrupting the overall microbiome balance.

5.4. Personalized Microbiome Medicine

The integration of artificial intelligence (AI) with microbiome research has opened new avenues for personalized medicine. AI-driven microbiome sequencing enables the development of customized treatment strategies tailored to individual microbial compositions.

From the findings of researchers at Rutgers University, AI models have been employed to redefine the core microbiome, facilitating the detection of microbial fingerprints linked to certain illnesses. This approach allows for the design of personalized therapeutic interventions that target dysbiosis and restore microbial balance.

Additionally, a research by Novielli et al. [119] highlights the function of explainable AI in the processing of microbiome data. The authors highlight how AI can enhance the interpretability of complex microbiome data, supporting the development of customised treatment strategies and the forecasting of illness outcomes.

Collectively, these new microbiome-based therapies offer tailored and targeted strategies that capitalise on the intricate relationship between the microbiota and the host, thereby revolutionising the treatment of cancer and immune disorders.

6. Challenges and Future Directions

The integration of microbiome science into immunology and oncology is reshaping therapeutic innovation, but this progress is tempered by conceptual, technical, and translational challenges. While mounting evidence links gut microbial communities to immune regulation and disease outcomes, translating these insights into safe, reproducible, and clinically effective therapies remains complex. Individual variability in microbiome composition, combined with the dynamic nature of host-microbe interactions, complicates the identification of universal biomarkers and consistent treatment protocols. Moreover, the development of scalable manufacturing practices, harmonized analytical methodologies, and robust regulatory frameworks is essential for advancing live biotherapeutics and microbiome-derived products. As interdisciplinary research deepens mechanistic understanding and refines intervention strategies,

this evolving field holds the ability to completely rethink how immune-mediated and oncologic illnesses are being managed—though with a trajectory that must remain both transformative and rigorously cautious.

6.1. Challenges in Translating Microbiome Research to Clinical Practice

Efforts to incorporate microbiome-based therapies into mainstream medicine have been complicated by considerable variability across individuals, both in terms of microbial composition and host responses. According to Zhernakova et al. [121], even among healthy populations, microbial profiles vary substantially depending on age, diet, geography, host genetics, and prior exposure to antibiotics, all of which influence disease susceptibility and therapeutic outcomes. Such inter-individual variability poses a major hurdle in designing broadly effective microbiome-based treatments.

Compounding this challenge is the absence of standardized procedures for the study of microbiomes, including inconsistencies in sample collection, sequencing depth, and bioinformatics pipelines. As noted by Marchesi et al. [122], reproducibility across studies is often compromised, impeding the establishment of robust microbial biomarkers and therapeutic targets. Additionally, the dynamic nature of the microbiome—subject to rapid shifts in response to diet, medications, or illness—further complicates clinical translation.

Regulatory frameworks governing microbiome interventions remain underdeveloped, particularly regarding live biotherapeutics and fecal microbiota transplantation (FMT). According to a regulatory review by El Hage et al. [123], inconsistencies in defining microbiota-based products, classifying them under existing pharmaceutical guidelines, and validating safety standards hinder their pathway to approval. The absence of universally accepted manufacturing and quality control standards for microbial therapeutics also limits scalability and clinical reproducibility. Moreover, ethical considerations regarding donor selection, long-term risks, and potential off-target effects are still being actively debated. These factors collectively delay the transition of microbiome science from academic research to bedside application, despite promising early results in specific therapeutic areas.

6.2. Future Research Directions

Future directions in microbiome research increasingly point toward the incorporation of high-throughput multi-omics technologies capable of providing a more thorough understanding of interactions between microbes and their hosts. From the findings of Lloyd-Price et al. [124], the incorporation of metagenomics, metabolomics, and proteomics not only enhances taxonomic resolution but also allows researchers to track functional pathways linked to immune regulation and disease progression. These multi-layered datasets are instrumental in identifying causal relationships rather than mere associations.

The use of machine learning algorithms and AI-based models to integrate multi-omic profiles with clinical phenotypes is poised to accelerate biomarker discovery and therapeutic prediction. According to Franzosa et al. [125], such integrative approaches have already shown promise in distinguishing microbiome signatures predictive of response to immune checkpoint inhibitors and autoimmune flare-ups. These models are expected to support the creation of more personalised and dynamic treatment regimens.

Additionally, expanding the clinical scope of microbiome interventions beyond autoimmune disorders and cancer represents a promising frontier. Research by Rooks and Garrett [126] indicates that modulating the gut microbiome may enhance graft survival in organ transplantation through the reduction of alloimmune responses. Similarly, according to Boehme et al. [127], specific microbial taxa and their metabolites have shown neuroprotective effects in preclinical models of neurodegenerative disorders such as Parkinson's and Alzheimer's, suggesting a potential therapeutic function in neurology. Age-related immune decline—immunosenescence—has also been linked to dysbiosis, as seen in Thevaranjan et al.'s work [128], indicating that specific microbiome modification may promote more healthful ageing. As the field matures, addressing these challenges through collaborative, interdisciplinary research will be essential to move microbiome science from theory to tangible clinical solutions.

7. Conclusion

Advances in microbiome science are rapidly reshaping our understanding of immune regulation and cancer therapy, demonstrating the gut microbiota's dual roles as a therapeutic ally and dynamic regulator in complex disease landscapes. It is now known that a major element influencing the onset, course, and resolution of autoimmune illnesses and cancers is the intricate relationship between microbial populations and the human immune system. From the findings of various authors cited throughout this review, it is clear that microbial signals—including metabolites, bacterial surface molecules, and secreted proteins—can influence not only local immune environments but also

systemic immunological homeostasis. This interdependence has laid the groundwork for novel interventions that harness the microbiome to enhance therapeutic responses, reduce treatment toxicity, and restore immune balance.

Yet, the full therapeutic promise of microbiome-based strategies rests on our capacity to accurately decipher the intricate relationships between microbes and hosts. Clinical translation continues to face hurdles related to interindividual microbiome variability, incomplete mechanistic understanding, and a lack of regulatory consensus on live microbial interventions. However, emerging tools such as multi-omics integration, AI-guided microbial profiling, and gene-editing approaches are poised to overcome these limitations. Future research will need to move beyond correlation and toward causation, refining our capacity to manipulate specific microbial pathways in a targeted and personalized manner.

Ultimately, the gut microbiome stands at the threshold of redefining immune and cancer therapies—not as a supplementary consideration, but as a foundational component of precision medicine. The integration of microbiome science into clinical practice will require sustained interdisciplinary collaboration, rigorous standardization, and a commitment to ethically and scientifically grounded innovation. As this field matures, its impact on patient care may well transform how immune and oncological disorders are understood and treated in the decades to come.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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