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Review

Microbiome Modulation in Lung Cancer Immunotherapy: Unveiling the Role of Respiratory and Gut Microbiota in the PD-1/PD-L1 Response

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Abstract

Lung cancer, the leading cause of cancer-related mortality worldwide, poses considerable therapeutic challenges due to the varied responses to programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors. Emerging highlight the pivotal role of host-microbiome interactions in modulating antitumor immunity and influencing clinical outcomes. This review examines how the respiratory and gut microbiota contribute to the immunosuppressive tumor microenvironment through dysbiosis-induced T-cell exhaustion and regulatory cell activation, while certain commensals facilitate dendritic cell-mediated recruitment of cytotoxic T lymphocytes. Additionally, this review explores the molecular mechanisms by which microbial metabolites, such as short-chain fatty acids, influence myeloid-derived suppressor cells. Therapeutically, microbiota-modulation strategies—such as tailored probiotic formulations and precision fecal microbiota transplantation—offer potential to enhance immunotherapy efficacy. This review provides a foundation for microbiome-guided immunotherapy, advocating for biomarker-driven patient stratification and the use of engineered microbial consortia to counteract therapeutic resistance. These findings pave the way for the integration of microbiome science into next-generation precision oncology.

Keywords: lung neoplasms; microbiota; immunotherapy; programmed cell death 1 receptor; programmed cell death 1 ligand 1

1. Introduction

Lung cancer, the most prevalent cancer globally, is associated with high mortality rates [1]. In 2022, 2.5 million new cases were diagnosed, representing 12.4% of all cancer cases worldwide, with 1.8 million deaths, accounting for 18.7% of cancer-related fatalities [2]. The 5-year survival rate for patients with lung cancer varies by region and stage, but remains below 20% in most countries [3]. While smoking is the leading risk factor, emerging evidence suggests that tobacco control measures could prevent over 1.6 million cases of lung cancer over a 20-year period [4]. Other established risk factors, such as viral infections, family history, genetic mutations, and environmental pollution, are also linked to the incidence of lung cancer [5].

Advances in tumor immunology have revealed the critical role of programmed death-1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), in immune evasion. Tumor cells express PD-L1 on their surface, which binds to PD-1 receptors on immune cells, inhibiting T-cell responses and allowing tumor cells to escape immune detection and elimination [6]. Additionally, tumor-derived immunosuppressive factors upregulate PD-1 expression on natural killer (NK) cells, impairing their surveillance function [7]. These mechanisms are especially relevant in non-small cell lung cancer (NSCLC), which constitutes more than 80% of all lung cancer cases [8,9]. PD-1/PD-L1 inhibitors are effective treatments for patients with metastatic NSCLC without epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) mutations [10]. Combining PD-1 inhibitors with adjuvant chemotherapy significantly increases the infiltration of T cells and B cells into the tumor microenvironment [11]. Although some patients experience survival benefits following immune checkpoint inhibitors (ICIs) [12,13], considerable variability in ICI efficacy persists across patients [14]. This variation may be influenced by the host's gut microbiota [15], with several studies demonstrating that the gut microbiota significantly impacts ICI effectiveness in patients with lung cancer [16–18]. For instance, patients with NSCLC who respond well to ICIs display distinct gut microbial profiles enriched in Firmicutes, *Actinobacteria*, and *Fusobacteria* [19]. Furthermore, probiotic supplementation has been associated with improved outcomes in patients treated with PD-1 inhibitors [20]. Moreover, advances in gene sequencing technologies have implicated the respiratory microbiota in the carcinogenesis of lung cancer [21], though its effect on ICI

responses remains unclear. Nonetheless, existing studies [22,23] suggest that the respiratory microbiota may play a role in modulating immune signaling within the tumor microenvironment (TME) (Fig. 1).

This review systematically investigates the dual role of the respiratory and gut microbiomes in lung cancer progression, focusing on characteristic changes in microbiota dysbiosis in patients with lung cancer and their dynamic relationship with clinical responses to ICIs. This review further explores how microbial metabolites influence the tumor immune microenvironment, impacting therapeutic outcomes, while assessing microbiota-targeting strategies aimed at enhancing immunotherapy. By synthesizing current knowledge on microbiome–host–tumor interactions,

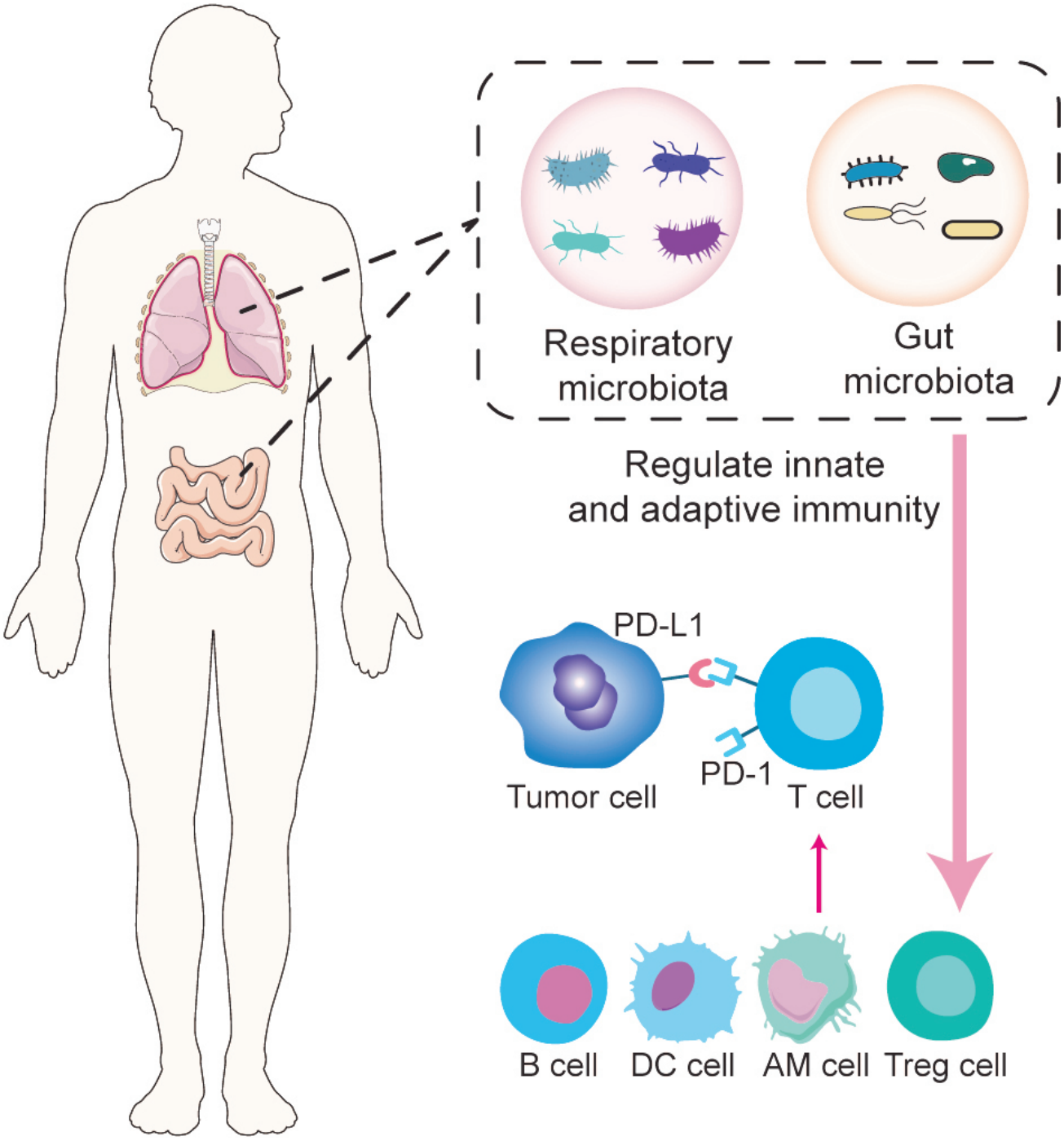

Fig. 1. Impact of gut and respiratory microbiota on immune checkpoint inhibitor (ICI) response. Alterations in the gut and respiratory microbiota can modulate both innate and adaptive immune systems, influencing the antitumor activity of immune-related cells and thereby affecting ICI efficacy. PD-1, programmed death-1; PD-L1, programmed death-ligand 1; AM, alveolar macrophage. This figure was created using Adobe Illustrator.

this review aims to establish a framework for developing microbiome-based precision immunotherapies.

2. Lung Microbiota and Immunotherapeutic Interventions in Lung Cancer

2.1 Influence of the Lung Microbiota on Tumorigenesis and Cancer Progression

In healthy individuals, a dynamic equilibrium exists between the lung microbiota and the host. Disruption of this balance can lead to alterations in microbiota composition, enabling bacteria to promote tumorigenesis by modulating the immune microenvironment [24,25]. A comparison of tumor and nontumor tissues from patients with lung cancer revealed a significant reduction in α-diversity in tumor tissues [26]. Notably, antibiotic use has been linked to an increased risk of lung cancer, further supporting the role of microbiota dysbiosis in carcinogenesis [27].

A landmark study comparing the microbiota distribution in bronchial samples from patients with lung cancer, nontumor tissues, and healthy controls showed that microbial richness and evenness followed this pattern: nontumor tissues, tumor tissues, and healthy controls. The relative abundance of *Streptococcus* and *Neisseria* genera decreased progressively, with *Streptococcus* showing moderate diagnostic value for lung cancer [28]. This study also demonstrated that in saliva and sputum samples, patients with lung cancer exhibited significantly higher relative abundances of *Granulicatella*, *Fastidiosa*, and *Streptococcus* compared to the control group [28]. Further research identified significant differences in the salivary microbiota between patients with adenocarcinoma and those with squamous cell carcinoma, with relative abundances of *Capnocytophaga*, *Selenomonas*, and *Veillonella* being notably different [29]. Similarly, a study using bronchoalveolar lavage fluid (BALF) samples to investigate the lung microbiota in relation to malignant tumors enrolled 28 participants (20 patients with lung cancer and 8 patients with benign diseases). Lung microbiota analysis revealed significantly greater relative abundances of *Veillonella* and *Megasphaera* genera in the lung cancer group compared to the benign disease group [30,31]. This alteration in microbiota structure may be closely linked to TME remodeling during carcinogenesis, suggesting that malignant transformation could induce microbial dysbiosis through changes in local physicochemical conditions [29]. Another study showed that, compared to nonmalignant lung tissues, the α-diversity index of lung cancer lesions was significantly lower, and the microbial composition correlated strongly with tumor clinical stage [26]. Data analysis indicated that in advanced-stage patients, the *Thermus* genus was specifically enriched in the TME, while Legionella abundance increased significantly in metastatic patients, suggesting that these microbial communities may influence lung cancer progression through specific mechanisms [26]. Moreover, a metagenomic analysis of BALF samples from 150 individuals (91 patients with lung cancer, 29 patients with nonmalignant lung diseases, and 30 healthy controls) revealed that the microbiota of patients with nonmalignant diseases was similar to that of patients with lung cancer but had lower microbial diversity than that of healthy individuals. Notably, *Bradyrhizobium japonicum* was present only in patients with lung cancer [32]. This study also suggested that microbial-specific biomarkers could aid in the diagnosis of patients for whom biopsy is not feasible [32]. Gomes *et al*. [33] analyzed 103 BALF samples and found that the microbiota in patients with squamous cell carcinoma was enriched in Proteobacteria and exhibited more diversity than that in adenocarcinoma individuals, particularly among males and heavy smokers.

The lung microbiota exhibits significant heterogeneity, with varying compositions across different regions of the lung in the same individual. Liu *et al*. [34] investigated the microbiota differences between healthy lung tissue, lung tissue on the same side as the cancer, and healthy lung tissue on the opposite side in patients with lung cancer. The study found a stepwise decrease in α-diversity, with *Staphylococcus* and *Dialister* being most abundant in healthy lung tissue, decreasing in healthy tissue opposite the cancer site, and showing the lowest abundance in lung tissue on the same side as the tumor. This study highlighted the critical role of microbiota balance in lung cancer development and progression. The composition of the lung microbiota may also be related to lung cancer prognosis. For instance, patients with advanced lung cancer exhibited a relatively high abundance of *Thermus*, while *Legionella* was more abundant in patients with metastasis [34]. Another study found that patients with lung cancer exhibiting brain metastasis had elevated *Pseudomonas* abundance, suggesting its potential as a diagnostic marker [35]. Peters *et al*. [36] conducted 16S rRNA gene sequencing on lung tumor and distal normal samples from 19 patients with NSCLC. Their findings showed that a higher abundance of Koribacteraceae in normal tissue was associated with better recurrence-free survival (RFS) and disease-free survival (DFS), whereas greater abundances of Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae were linked to poorer RFS and DFS. These results suggest that alterations in the airway and lung microbiota composition may serve as prognostic indicators for lung cancer [36].

2.2 Microbiota-driven Modulation of Immune Checkpoints in Lung Cancer Immunotherapy

The antitumor immune system is typically capable of identifying and eliminating a small number of cancer cells within the body. However, as cancer progresses, tumor cells may evade immune surveillance [37]. Immune checkpoint inhibition is a major mechanism of tumor immune evasion [38]. Notably, microbial dysbiosis in local tissues can synergize with checkpoint pathways, exacerbating immunosuppression. As summarized in Table 1 (Ref. [39–

45]), studies have revealed that specific microbiota components modulate antitumor immunity by altering immune cell functions. For instance, Gollwitzer *et al*. [39] demonstrated that, in the first two weeks after birth, pulmonary bacterial load increased, and the microbial composition shifted from a dominance of Proteobacteria and Firmicutes to an overrepresentation of *Bacteroidetes*. This shift induced a highly immunosuppressive Helios-Treg cell subset, reducing the body's response to airborne allergens. The development of this Treg subset relied on the upregulation of PD-L1 expression in dendritic cells. In the absence of microbial colonization or blockade of PD-L1 during this period, susceptibility to allergic reactions persisted into adulthood. Furthermore, adoptive transfer of adult Treg cells into newborn mice reversed this hyperreactive allergic phenotype [39]. Herbst *et al*. [46] also reported that the absence of the lung microbiota led to immune dysregulation, triggering excessive allergic responses, whereas restoration of the microbiota helped establish an immune-tolerant microenvironment by modulating plasmacytoid dendritic cell and alveolar macrophage (AM) development and function. These studies suggest that the lung utilizes Tregs and macrophages to maintain a low-reactivity state to inhaled antigens, representing a unique immune tolerance mechanism. This tolerant environment may be exploited by metastatic tumor cells, establishing an immune evasion sanctuary [47]. Le Noci *et al*. [40] observed that antibiotic treatment (vancomycin/neomycin) in mice reduced the bacterial load in lung tissue, which was accompanied by a decrease in Treg cell numbers and an increase in T cell and NK cell activation, significantly reducing melanoma B16 lung metastasis. Further research demonstrated that aerosolized *Lactobacillus rhamnosus* significantly enhanced the immune response against B16 lung metastasis [40].

Mycobacterium tuberculosis (MTB) infection has been shown to contribute to lung cancer development, primarily through mechanisms involving inflammation, lung fibrosis, and immunosuppression [48,49]. In the early stages of MTB infection, immune responses driven by type 1 helper T (Th1) cells, along with the secretion of IFN-γ and TNF-α, facilitate bacterial survival. However, immune evasion mechanisms, including checkpoint inhibition, promote the persistence of latent MTB infection [28,41]. In lung cancer tissues, an increased abundance of *Veillonella* has been linked to the inhibition of tumor-infiltrating T lymphocyte recruitment and suppression of $CD3^+$ and $CD4^+$ T lymphocytes in the peripheral immune microenvironment [42]. A study of 49 participants revealed that patients with higher respiratory microbiota loads showed diminished immune responses to lipopolysaccharides in AMs [43]. In contrast, commensal bacteria mitigate excessive immunosuppression by inhibiting M2 macrophage polarization and limiting CCL24 production in AMs, thereby preserving $\gamma\delta$ T-cell-mediated antitumor immunity—a mechanism that maintains a balance between immune tolerance and surveillance in the lungs [44]. Certain lung microbiota have been identified as activators of immune responses. For instance, compared to healthy controls, patients with NSCLC exhibit significantly enhanced Th1 and Th17 responses against *Streptococcus salivarius* and *Streptococcus agalactiae* [45].

These findings underscore the critical role of the lung microbiota in regulating the pulmonary immune environment. Shifts in microbial diversity not only modulate key molecules such as PD-L1 but also influence various populations of innate and adaptive immune cells. Thus, modifying the lung microbiota holds potential for reversing the immunosuppressive state within the pulmonary TME, potentially augmenting antitumor immune responses. However, the precise role of the lung microbiota in lung cancer remains an area for further investigation.

3. The Gut Microbiota and Its Role in the Efficacy of Immunotherapy for Lung Cancer

The role of the gut microbiota in cancer immunotherapy has garnered considerable attention [50]. Alterations in the gut microbiota can influence the activity of innate and adaptive immune cells within the TME, thereby modulating the antitumor efficacy of immune cells and affecting the therapeutic outcomes of ICIs (Fig. 2) [51]. Moreover, oral administration of probiotics combined with ICIs has been shown to significantly enhance antitumor efficacy [52], highlighting the critical role of the gut microbiota in tumor immunotherapy. This section reviews key gut microbiota components that impact the effectiveness of immunosuppressive agents in lung cancer treatment.

3.1 Lactobacillus Drives Dendritic Cell Maturation and Th1 Immunity

Lactobacillus rhamnosus GG, one of the most extensively studied probiotics, has been shown to inhibit tumor progression [53]. It significantly increases the expression of dendritic cell maturation markers such as CD40 and major histocompatibility complex class II (MHC II), as well as the secretion of cytokines like IL-10, tumor necrosis factor-α (TNF-α), and IL-12, thereby activating dendritic cells and enhancing T-cell immune responses [54]. This study also highlighted the dose-dependent immune-enhancing effects of *L. rhamnosus* GG. Exposure of dendritic cells to low doses (5:1 or 10:1, LGG:cell ratio) induced stronger Th1 polarization in T cells, resulting in enhanced antitumor efficacy [54]. Additionally, *L. rhamnosus* GG not only enhances dendritic cell function to boost immune responses but also reduces the number of $CD11c^-$MHC II^+ cells in tumors, activates the cyclic GMP–AMP synthase (cGAS)/stimulator of interferon genes (STING)/TANK-binding kinase 1 (TBK1)/interferon regulatory factor 7 (IRF7) axis, and induces interferon-β (IFN-β) production in dendritic cells while enriching *L. murinus* and *B. uniformis* in the gut microbiota [55]. Elevated MHC II levels have been shown to inhibit $CD8^+$ T-cell activity, with high

Table 1. Lung microbiota and their potential roles in immunotherapy.

Author	Microbial focus	Sample type	Major findings	Reference
Le Noci V *et al*.	*Lactobacillus rhamnosus*	Bronchoalveolar lavage fluid	Antibiotic treatment enhances the activity of pulmonary T cells and NK cells, while nebulized *Lactobacillus rhamnosus* strengthens the immune response against B16 lung metastasis.	[40]
Gollwitzer ES *et al*.	Proteobacteria, Firmicutes, Bacteroidetes	Bronchoalveolar lavage fluid	The microbiota, initially dominated by Proteobacteria and Firmicutes, gradually shifts toward *Bacteroidetes*, resulting in the emergence of Treg subsets and subsequent immunosuppression.	[39]
Chang ST *et al*.	*Mycobacterium tuberculosis*	-	MTB exploits the host's Th1 immune response and associated cytokines (IFN-γ and TNF-α) to evade host-mediated killing, promote immune evasion, and hijack immune checkpoint pathways.	[41]
Zeng W *et al*.	*Veillonella*	Bronchoalveolar lavage fluid	Veillonella inhibits the recruitment of tumor-infiltrating T lymphocytes, reduces the proportion of $CD3^+$ and $CD4^+$ T cells in the peripheral immune microenvironment, thereby promoting immunosuppression.	[42]
Segal LN *et al*.	-	Bronchoalveolar lavage fluid	A high respiratory microbiota burden impairs the immune response of alveolar macrophages to lipopolysaccharide in the lungs.	[43]
Cheng M *et al*.	-	Lung mononuclear cell	Commensal microbiota sustain $\gamma\delta$ T-cell-mediated antitumor immunity by inhibiting M2 macrophage polarization and restricting CCL24 production in alveolar macrophages.	[44]
Ma QY *et al*.	*Streptococcus salivarius*, *Streptococcus agalactiae*	Resected tumor sample from consenting NSCLC patients	In NSCLC patients, lung cancer tissues show significantly upregulated Th1 and Th17 cell responses to Streptococcus salivarius and Streptococcus agalactiae, with these responses predominantly enriched in $CXCR5^+CD4^+$ T cells.	[45]

NK, natural killer; MTB, *Mycobacterium tuberculosis*; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; CCL24, C-C motif chemokine ligand 24; NSCLC, non-small cell lung cancer; $CXCR5^+$, C-X-C chemokine receptor type 5–positive.

MHC II levels positively correlating with tumor cell growth. Consequently, the immune-enhancing effects of *L. rhamnosus* GG may be linked to the suppression of CD11c-MHC II$^+$ cell numbers [55]. Additionally, *L. murinus* has been reported to promote IL-12 expression in dendritic cells and decrease OX40 expression, thereby further enhancing immune system activation. These findings suggest that the immune activation effects of *L. rhamnosus* GG may be associated with changes in the gut microbiota composition [56]. Moreover, *L. rhamnosus* GG acts as a delivery vector, entering the hypoxic regions of tumors to effectively deliver the CRISPR/Cas9 system, generating ROS, inducing immunogenic cell death, and inhibiting lung metastasis of cancer cells [57]. *L. rhamnosus* GG increases the infiltration of B cells, natural killer (NK) cells, and myeloid cells in the lungs while reducing the number of Treg cells, resulting in a reduction in the number, diameter, and area of lung tumor nodules [58]. Furthermore, *L. rhamnosus* Probio-M9 increases the abundance of beneficial microorganisms such as *Bifidobacterium pseudolongum* and *Parabacteroides distasonis*, thereby enhancing the efficacy of anti-PD-1 immunotherapy [59]. This study also suggested that *L. rhamnosus* Probio-M9 is enriched in pathways related to carbohydrate degradation, vitamin synthesis, and amino acid biosynthesis, all of which are associated with immune enhancement in the host [60,61]. Therefore, *L. rhamnosus* Probio-M9 may improve the efficacy of anti-PD-1 immunotherapy by enriching these pathways.

3.2 Bifidobacterium Boosts Interferon-γ and CD8$^+$ T Cell Attack

Bifidobacterium is a common microorganism in the gut microbiota, and its role in enhancing ICI treatment has been extensively studied. Lee *et al*. [62] analyzed fecal samples from 96 patients with NSCLC and 139 healthy controls, revealing that the abundance of *B. bifidum* was significantly higher in responders to ICI treatment than in nonresponders. Moreover, oral administration of *B. bifidum* promoted IFN-γ secretion, enhancing its antitumor effect in combination with PD-1 inhibitors [62]. In mice treated with anti-PD-L1 therapy, those showing a better response to ICI treatment had higher *Bifidobacterium* abundance in their feces and more pronounced infiltration of CD8$^+$ T cells in tumor tissues, suggesting that *Bifidobacterium* may mediate immune responses that influence tumor growth [52]. Additionally, fecal transplantation from mice with better ICI responses to those with poorer responses resulted in a significant decrease in tumor growth rate, increased CD8$^+$ T cell infiltration, enhanced IFN-γ secretion, and improved dendritic cell function [52]. Additionally, the presence of *Bifidobacterium longum* in the fecal microbiota correlates with effective anti-PD-1 therapy. Fecal microbiota transplantation (FMT) into germ-free mice enhanced the efficacy of immunotherapy and slowed tumor growth [51]. However, some *Bifidobacterium* strains do not synergize with anti-PD-1 therapy [63]. *B. longum* has been reported to improve tumor control after anti-PD-L1 therapy [64], but another study found that although *B. longum* BNCC185354-treated mice exhibited tumor-suppressive effects, when combined with pembrolizumab, it reduced the antitumor effects of the drug [65]. These findings suggest that while certain *Bifidobacterium* strains may enhance ICI efficacy, the effects can vary even within the same species. A study involving fecal samples from 21 patients with NSCLC and 22 healthy controls revealed that *B. breve* was enriched in patients who responded to anti-PD-1 treatment. Patients with detectable *B. breve* in their feces had longer median progression-free survival (PFS), and the presence of *B. breve* proved to be a more significant predictor of patient prognosis than PD-L1 expression levels [66]. Further research demonstrated that mice lacking *B. breve* had fewer SVY-reactive T cells and faster tumor growth compared to mice colonized with *B. breve*. This effect was attributed to the similarity between the SVY epitope antigen in *B. breve* and the SIY antigen on tumor cell surfaces, enabling T cells to recognize both and enhance the antitumor immune response [64].

3.3 Bacteroidetes Enhances Memory CD8$^+$ T and Natural Killer Cell Responses

Bacteroidetes are a vital group of probiotics in the human gut, with studies indicating their ability to inhibit the onset of various immune-related diseases, including pneumonia [67]. The genus *Alistipes*, a member of the Bacteroidetes phylum, has been shown to enhance the efficacy of cancer immunotherapy [68]. The abundance of *Alistipes* in the gut microbiota has been linked to longer PFS in patients with NSCLC undergoing ICI therapy [69]. *Alistipes indistinctus* is significantly enriched in responders to immunotherapy in patients with NSCLC, thereby enhancing ICI effectiveness [16]. A high abundance of *A. indistinctus* was strongly correlated with greater clinical benefits in patients with advanced lung cancer (HR = 3.08), suggesting its role in enhancing antitumor responses by modulating the gut immune microenvironment [16]. Similarly, in Chinese patients with NSCLC treated with the PD-1 inhibitor nivolumab, responders exhibited significantly higher levels of *Alistipes* putredinis in their gut microbiota [70]. Flow cytometry further revealed a higher frequency of memory CD8$^+$ T cells and NK cells in the peripheral blood of these responders. These findings suggest that *Alistipes* putredinis may enhance ICI efficacy by indirectly activating both adaptive immunity and innate immunity pathways [70]. In patients with lung cancer treated with PD-1 antagonists, an increased ratio of Bacteroidetes to Firmicutes was associated with diarrhea following PD-1 antagonism treatment [71].

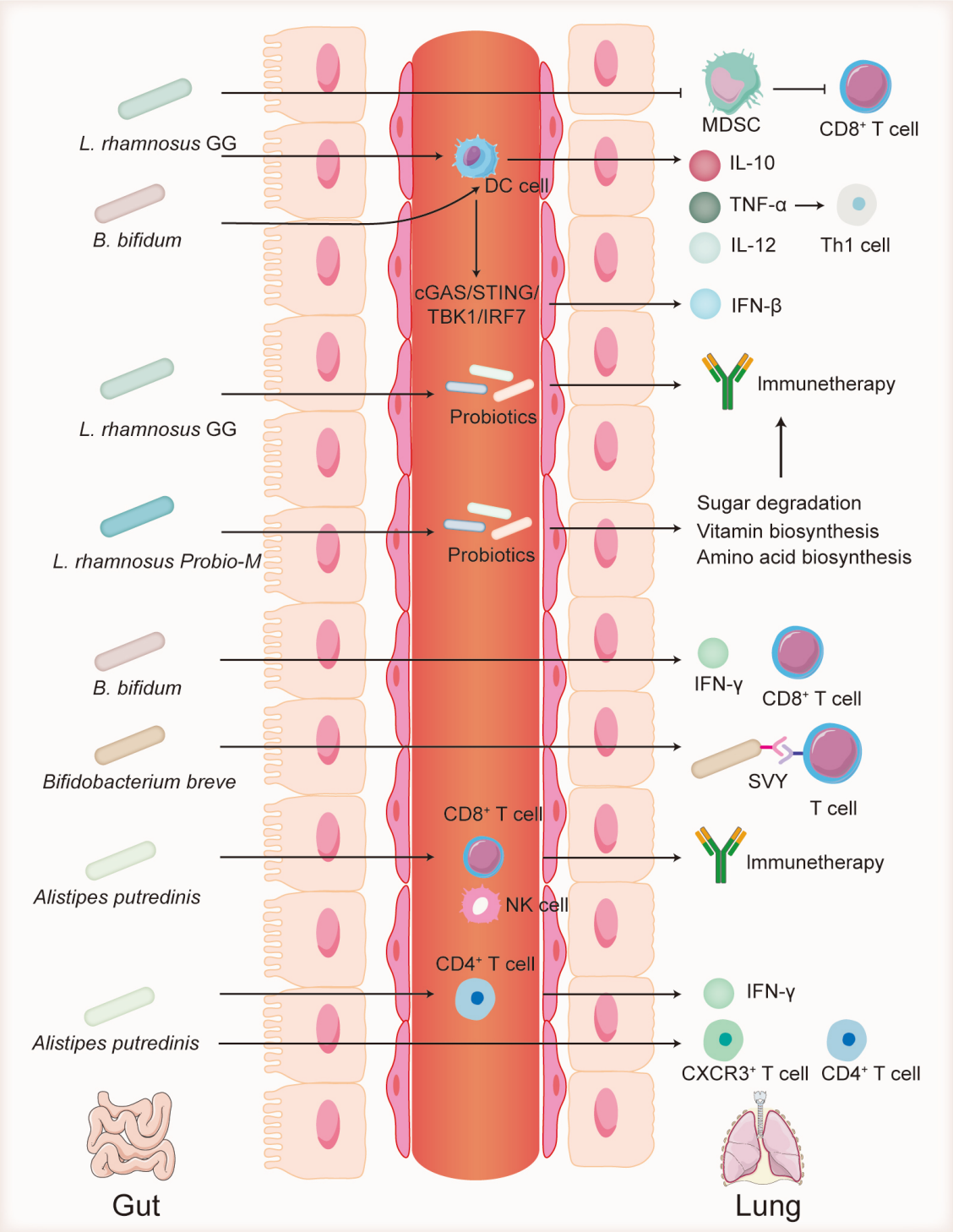

Fig. 2. Role of the gut microbiota in immunotherapy. *Lactobacillus rhamnosus* GG inhibits MDSCs, which suppress $CD8^+$ T cells. *L. rhamnosus GG* also alters probiotic abundance, promotes dendritic cell activation, and enhances cytokine secretion, thereby boosting Th1 cell responses. *Lactobacillus rhamnosus Probio-M* modulates probiotic populations and regulates metabolic pathways related to sugar, vitamin, and amino acid synthesis. *Bifidobacterium bifidum* stimulates IFN-γ secretion and activates $CD8^+$ T cells. *Bifidobacterium breve* enhances T-cell activation *via* the SVY epitope. *Alistipes putredinis* activates $CD8^+$ T cells, NK cells, $CD4^+$ T cells, and $CXCR3^+$ T cells. Through these mechanisms, the gut microbiota activates both innate and adaptive immune systems, thereby enhancing the efficacy of ICIs. MDSCs, myeloid derived suppressor cells; IFN-γ, interferon-γ; SVY, the peptide epitope SVYRYYGL; NK, natural killer; $CXCR3^+$, C-X-C chemokine receptor 3-positive; IL-10, interleukin-10; TNF-α, tumor necrosis factor-α. This figure was created using Adobe Illustrator.

3.4 Exploring the Impact of Other Microbial Communities on Lung Cancer Immunotherapy

Akkermansia muciniphila, a strict anaerobic symbiotic bacterium from the Verrucomicrobia *phylum*, participates in host metabolic regulation by degrading the intestinal mucus layer and enhancing barrier function [72]. It is reported that [73] the abundance of *A. muciniphila* in fecal samples from advanced NSCLC and renal cell carcinoma individuals responsive to PD-1 therapy was significantly higher than in nonresponders. Similarly, Matson *et al.* [51] observed a trend of *A. muciniphila* enrichment in the gut of responders within a melanoma patient cohort. Mechanistic studies have shown that *A. muciniphila* activates antitumor immunity by stimulating $CD4^+$ T cells to secrete high levels of interferon-γ (IFN-γ) [52]. The Huoxue Yiqi Recipe-2 has also been reported to enhance the therapeutic effect of PD-L1 antibodies by increasing *A. muciniphila* levels, thereby exerting antitumor effects in lung cancer [74]. *Faecalibacterium*, an anaerobic bacterium and one of the predominant butyrate-producing species in the human gut, has long been regarded as a biological marker of human health and a dominant strain that inhibits inflammation progression [75]. *Faecalibacterium* plays a pivotal role in the immune microenvironment by enhancing antigen-presenting capacity and T-cell function within the TME, thereby boosting antitumor immune responses [76]. *Faecalibacterium prausnitzii* strain EXL01 enhances T-cell activation in the presence of immune-checkpoint inhibitors and restores antitumor responsiveness to the therapy [77]. In a mouse model of natural-killer/T-cell lymphoma, oral administration of *Faecalibacterium prausnitzii* or its metabolite butyrate together with an anti-PD-L1 monoclonal antibody markedly suppressed tumor growth, increased intratumoral cytotoxic $CD8^+$ T cells, and overcame the ICI hyporesponsiveness induced by antibiotics [78].

4. Respiratory Microbiota: Shaping Lung Cancer Progression and Immunotherapy Outcomes

In the adult respiratory tract, bacterial communities are partitioned along a clear vertical gradient, with total biomass falling steadily from the upper to the lower airway. The anterior nares are dominated by the phyla Actinobacteria and Firmicutes [79]. In the nasopharynx, Firmicutes and Proteobacteria expand in relative abundance at the expense of Actinobacteria [80], whereas the oropharynx is chiefly colonized by the phylum Bacteroidetes [80]. In healthy individuals, the bacterial burden of the lower airway is just 1/100 to 1/10,000 of that in the upper airway. Here, Firmicutes, Bacteroidetes and Proteobacteria prevail, with *Prevotella*, *Streptococcus* and *Veillonella* as the most abundant genera [81]. Lung cancer associated dysbiosis is characterized by enrichment of Firmicutes and the candidate phylum TM7, alongside depletion of Proteobacteria [31]. Although *Prevotella* remains numerically dominant at the genus level, its relative abundance decreases, while *Veillonella* becomes more prevalent [31]. A diverse community structure—as opposed to domination by a single strain—appears to support the efficacy of ICIs, with *Bacillus* playing a particularly important role. By contrast, *Sphingomonas* and *Sediminibacterium* may foster post-ICI tumour progression through reprogramming of lipid and essential-amino-acid catabolism [82]. Metabolites released by the microbiota reshape the lower-airway immune milieu by driving the secretion of inflammatory cytokines and chemokines; this response is accompanied by reduced $CD8^+$ effector T-cell and M1-like macrophage infiltration in malignant lesions [82]. In a cohort of 56 patients with advanced NSCLC, responders to anti-PD-1 therapy showed significantly higher relative abundances of *Staphylococcus* and *Streptomyces* in bronchoalveolar-lavage fluid (BALF; $\geq$3%, $p < 0.05$) as well as elevated levels of tryptophan-derived bacterial metabolites, each tightly linked to distinct genera (VIP >1, $p < 0.05$) [83]. These findings suggest that PD-1 blockade may modulate therapeutic efficacy through a "microbiota–tryptophan axis" in the lower airway [83]. Yu *et al.* [84] reported that BALF from patients with checkpoint-inhibitor pneumonitis contained increased abundances of *Vibrio metschnikovii* and *Mangrovibacter plantisponsors*; the co-occurring intermediate metabolite lauroylcarnitine markedly enhanced IFN-γ and TNF-α production by human and murine $CD4^+$/$CD8^+$ T cells *in vitro*. Moreover, in early-stage NSCLC, distinct pre-operative BALF signatures predicted post-surgical recurrence, were associated with up-regulation of cell-proliferation and epithelial–mesenchymal-transition genes, and thus may directly influence tumour biology and patient prognosis [85].

5. Mechanisms of Microbial Influence on Pulmonary Immunity

Defensive cells in the respiratory system continuously monitor the airway microenvironment to protect the host from pathogenic microbial invasion [86]. A core function of these cells is to prevent excessive inflammatory responses to nonpathogenic environmental factors. AMs and dendritic cells maintain the immune hyporesponsiveness characteristic of the lungs by inducing Treg cell differentiation [87] and secreting immune-regulatory factors such as prostaglandin E2, transforming growth factor-β, and interleukin-10 [88]. The symbiotic microbiota colonizing the respiratory tract plays a critical role in regulating local immune cell function, thereby maintaining the balance of immune tolerance.

5.1 Microbial Interactions With Pulmonary Immune Cells: Implications for Immune Tolerance

Pattern recognition receptors (PRRs) expressed on respiratory epithelial cells and antigen-presenting cells, including AMs and dendritic cells, specifically recognize molecular signals from both host and microbial sources

[89]. These receptor families include Toll-like receptors, NOD-like receptors, and C-type lectin receptors [90]. Upon binding to their ligands, these receptors activate immune-related genes that encode inflammatory mediators and type I interferons, initiating both innate and adaptive immune responses [91,92]. The innate immune system integrates multiple signals to distinguish "danger" from "safe" signals: (1) Symbiotic bacteria, isolated by the mucus barrier, do not directly engage PRRs on epithelial cells, whereas pathogens breach this barrier *via* virulence factors to trigger immune responses [93,94]; (2) the spatial distribution of PRRs on the mucosal surface is specific, physically separated from sites of symbiotic bacterial colonization [95]; and (3) immune cells, through cross-talk mechanisms, combine PRR signals with cytokine networks in the microenvironment (e.g., negative regulation by IL-10), dynamically modulating inflammatory response intensity [96]. Through continuous exposure to microbial signals, respiratory immune cells develop unique response patterns. After repeated stimulation by TLR ligands, antigen-presenting cells exhibit a tolerant phenotype, characterized by reduced secretion of proinflammatory cytokines [97]. Pulmonary dendritic cells promote B-cell class switching *via* TLR signaling, differentiating into plasma cells that secrete IgA, thus enhancing mucosal immune tolerance [98]. Additionally, AMs regulate anti-inflammatory mediator synthesis through metabolic reprogramming to maintain tissue homeostasis [99]. These adaptive changes emphasize the critical role of interactions between the lung microbiota and the host immune system in establishing the immune-tolerant microenvironment of the lungs.

5.2 Microbial Metabolites and Their Role in Immune Regulation

The microbiome influences metabolic balance by regulating the host's detoxification enzyme systems and nutrient absorption pathways [100]. Notably, changes in the composition of specific microbiota are strongly linked to carcinogenic metabolic processes, such as increased aldehyde dehydrogenase activity and enhanced synthesis of deoxycholic acid [101]. Emerging evidence highlights CD36—a fatty acid translocase and PRR—as a key molecular mediator at the host-microbe-cancer interface [102]. This multifunctional transmembrane protein is aberrantly overexpressed in lung cancer [103,104]. As a pathogen-associated molecular pattern receptor, CD36 activates pro-carcinogenic inflammatory signals [105]. Additionally, CD36 has been shown to facilitate lipid uptake, promoting lipid oxidative metabolism in tumor-infiltrating myeloid derived suppressor cells (MDSCs) and enhancing their immunosuppressive effects.

Notably, the microbial metabolite axis intersects with CD36 regulation through free fatty acid receptor 2 (FFAR2) signaling. Genetic ablation of FFAR2 significantly reduces CD36 expression [106]. The study further suggested that short chain fatty acids (SCFAs) in the TME activate FFAR2 receptors on MDSCs, driving L-arginine consumption in the microenvironment, which, in turn, accelerates urate-induced lung cancer progression [106]. Tumor models in FFAR2 knockout mice showed a notable decrease in MDSC accumulation and an increase in $CD4^+$ and $CD8^+$ T-cell infiltration within the TME [106]. These findings indicate that microbial metabolites, particularly SCFAs, may promote immune suppression by elevating CD36 expression and activating MDSCs. Furthermore, studies of the lower respiratory tract biofilm microenvironment have revealed that SCFAs produced by anaerobic bacteria enhance the expression of the transcription factor forkhead box P3 (FoxP3) in $CD4^+$ T cells *via* epigenetic modifications, promoting Treg cell differentiation and fostering immune tolerance [107]. SCFAs also suppress IFN-γ secretion by T lymphocytes and reduce the tumor-killing capacity of cytotoxic T cells [108]. This metabolic-immune axis reprogramming provides new insights into how the microbiota influences antitumor immune responses.

6. Harnessing the Gut Microbiota to Augment the Efficacy of ICIs in Lung Cancer

Recent population-based studies have systematically delineated the tight relationship between gut microbiome composition and the therapeutic efficacy of ICIs in patients with NSCLC. A pioneering prospective single-center cohort from China (n = 34) first showed that higher baseline gut α/β diversity, together with enrichment of *Akkermansia muciniphila* and Ruminococcaceae, was significantly associated with improved objective response rate, PFS, and overall survival [66]. A subsequent multicenter prospective study in Japan (n = 70) confirmed that patients harboring butyrate-producing taxa—such as *Faecalibacterium* and members of the order *Clostridiales*—derived greater clinical benefit, whereas prior antibiotic exposure attenuated this association [109]. Another single-center Chinese cohort (n = 85) further demonstrated that differences in gut β diversity and in tryptophan/purine metabolic pathways distinguished ICI responders from non-responders [110]. In a multicenter US cohort (n = 65), genus-level interaction networks linked enrichment of *Bifidobacterium* and *Collinsella* to positive outcomes, while excessive *Prevotella* interactions predicted poor responses [111]. A prospective multicenter study from Thailand (n = 95) revealed a high-fat diet–*Firmicutes* enrichment axis associated with reduced efficacy and reaffirmed the protective role of *A. muciniphila* [112]. Most recently, a large multinational cohort (n = 245) integrated species-level co-abundance networks to construct an ecological score that predicted overall survival with an AUROC of 0.78 and identified *Bacteroides fragilis* and *Faecalibacterium prausnitzii* as key protective species [113]. Collectively, these lines of evidence indicate that baseline gut microbial diversity and the abundance of specific commensal taxa serve as

robust population-level biomarkers for predicting ICI efficacy in NSCLC. They provide a compelling rationale for microbiome-based patient stratification and the personalized optimization of immunotherapy in clinical practice.

Compared to healthy individuals, patients with lung cancer exhibit significant differences in their gut microbiota profiles [114], suggesting that the microbiota may influence both lung cancer prognosis and treatment efficacy. These differences imply that the gut microbiota not only potentially impacts cancer development by altering the immune microenvironment but also plays a pivotal role in modulating the effectiveness of immunotherapy. For example, a prospective analysis of 63 patients with advanced NSCLC revealed distinct variations in gut microbiota composition, functional protein families, and KEGG metabolic pathways between patients with PFS $\geq$6 months and those with PFS $<$6 months [115]. Additionally, the β-diversity of fecal microbiota in patients receiving PD-1 inhibitors was strongly correlated with their response to anti-PD-1 immunotherapy [115]. In patients with NSCLC responding to nivolumab, the gut microbiota composition was more stable and diverse, with higher bacterial diversity correlating with significantly better PFS compared to patients with low diversity. Multicolor flow cytometry analysis revealed that patients with greater microbiota diversity had a higher proportion of peripheral blood $CD8^+$ T cells and NK cell subpopulations with a unique memory phenotype [116]. Further studies supported these findings. Ren *et al*. [117] analyzed 71 stool samples from 41 patients with advanced NSCLC before immune checkpoint blockade (ICB) treatment and reported that increased microbiota diversity was significantly associated with better responses to ICIs. Responders had significantly higher levels of Bacteroides species in their feces, and FMT enhanced the effectiveness of immunotherapy. An analysis of the gut microbiomes of 96 patients with NSCLC found that responders had significantly greater levels of *Bifidobacterium*. In mice treated with *Bifidobacterium* strains, the bacteria stimulated the host immune response and synergized with PD-1 blockade or oxaliplatin treatment, reducing tumor burden [62]. Retrospective analyses have shown that treatment with *Clostridium butyricum* MIYAIRI 588 strain significantly extends PFS (HR = 0.46, p = 0.004) and OS (HR = 0.33, p = 0.001) in patients with advanced NSCLC receiving ICB therapy, suggesting that CBM588 may enhance ICB efficacy by regulating the gut microbiota and improving survival outcomes in patients with late-stage lung cancer. Similarly, a meta-analysis found that patients with NSCLC who used probiotics during ICI therapy had significantly longer PFS and OS, as well as higher objective response rates and disease control rates.

In addition, components derived from traditional Chinese medicine, including monomeric compounds and polysaccharide extracts, have been reported to regulate the gut microbiota and enhance immune function, thereby playing an important role in the prevention and treatment of lung cancer. For example, Zengshengping, a widely used antitumor TCM compound in clinics, is a herbal formulation composed of *Sophora tonkinensis* Gagnep, *Polygonum bistorta* L, *Prunella vulgaris* L, *Sonchus brachyotus* L, *Dictamnus dasycarpus* Turcz and *Dioscorea bulbifera* L [118]. It has been shown to significantly increase the diversity and richness of the gut microbiota in Lewis lung cancer model mice, elevating the concentration of secretory immunoglobulin A in BALF, protecting the intestinal mucosa, and regulating the abundance of beneficial gut microbiota, ultimately improving lung cancer symptoms [118]. Similarly, Huang *et al*. [119] demonstrated that ginseng polysaccharides combined with αPD-1 monoclonal antibody treatment enhanced the response to PD-1 inhibitors in an NSCLC mouse model that had undergone FMT. Microbiota analysis revealed that, in clinical responders to anti-PD-1 treatment, the abundance of *Parabacteroides distasonis* and *Bacteroides vulgatus* was significantly higher than in nonresponders, and combination treatment reshaped the microbiota of nonresponders to resemble that of responders [119].

These studies highlight the critical role of the gut microbiota in lung cancer immunotherapy, not only by modulating immune responses but also by providing potential predictive biomarkers for clinical outcomes based on microbiota characteristics. Therefore, modulating the gut microbiota may emerge as an important strategy to enhance the effectiveness of immunotherapy.

7. Conclusion and Future Perspectives

Accumulating evidence suggests that both the resident lung microbiota and the gut microbiome act as critical dynamic regulators of antitumor immunity in lung cancer. Dysbiosis within the lung microbiota, characterized by reduced alpha diversity, increased relative abundances of genera such as *Veillonella* and *Thermus* and spatial heterogeneity even within the same organ, has been closely linked to tumor initiation, progression and variable responses to inhibition of PD-1 and CTLA-4. Conversely, restoration of pulmonary microbial homeostasis can reprogram local antigen presenting cells and regulatory T cell subsets to reverse immune evasion. In the gut, commensal taxa including *Lactobacillus*, *Bifidobacterium*, *Alistipes*, *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* have been shown to promote dendritic cell maturation, Th1 polarization, interferon gamma production and infiltration of cytotoxic T lymphocytes and natural killer cells, collectively improving tumor control and survival. Mechanistically, the lung and gut microbiota modulate antitumor immunity via pattern recognition receptor signaling, metabolic reprogramming and epigenetic regulation of T cell differentiation.

Although research on the microbiome associated with lung cancer is still in its infancy, emerging evidence

shows that it can meaningfully modulate responses to immunotherapy. Future work should use longitudinal multi-omics cohorts to chart the temporal dynamics of pulmonary microbial communities during disease progression and treatment, and to dissect the functional pathways of both dominant and rare taxa so as to identify microbes that enhance the efficacy of ICIs. Synthetic biology and genome editing can then create engineered probiotic strains and test their ability to amplify ICI activity. It is equally important to incorporate the gut microbiome into a personalized intervention framework; by considering each patient's antibiotic exposure, researchers can design precisely matched FMT protocols and evaluate their efficacy and safety in randomized controlled trials. Ultimately, integrating microbiome profiles with host immune parameters and clinical data into interpretable predictive models should allow real-time risk assessment and intervention planning, thereby advancing the clinical translation of microbiome modulation in lung cancer immunotherapy.

Author Contributions

YYX wrote the manuscript. QQL and HW conceived and designed the study. YYX, YXT, HBP and ZJW reviewed the literature and constructed the figures and tables. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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