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The respiratory microbiota in lung cancer: bridging dysbiosis, immunomodulatory networks, and therapeutic opportunities

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Highlights:

- Respiratory dysbiosis drives lung cancer via three integrated pathways.
- Respiratory microbiota signatures predict diagnosis, staging, and therapy response.
- Targeting the respiratory microbiota shows preclinical promise.
- Respiratory microbiota translation requires multi-omics and clinical validation.

Abstract: Lung cancer remains the leading cause of cancer-related mortality worldwide, with limited therapeutic responses and frequent acquired resistance. The respiratory microbiota has recently been recognized as an important regulator of lung cancer. Although most research has concentrated on the gut microbiota, its composition differs substantially from that of the lung microbiota. Emerging evidence indicates that dysbiosis of the airway and intratumoral microbiome contributes to lung oncogenesis, disease progression, and immunotherapeutic outcomes through multiple mechanisms. Therefore, elucidating how microorganisms residing in the respiratory tract affect lung carcinoma development and treatment response may be essential for predicting cancer risk and enhancing therapeutic efficacy and safety. In this review, we discuss the compositional characteristics of the respiratory microbiome, its association with lung cancer, and the potential mechanisms through which the respiratory microbiota contributes to carcinogenesis. We also summarize its potential applications in diagnosis, subtyping, staging, and prediction of treatment response, and explore the feasibility of therapeutic microbiome modulation for developing lung cancer prevention strategies and optimizing treatment.

Keywords: lung cancer; respiratory microbiome; dysbiosis; tumor microenvironment; immunotherapy

1. Introduction

Globally, lung cancer caused 2.48 million incident cases and 1.82 million fatalities in 2022, representing 12.4% and 18.6% of total cases and deaths, and it remained the most common and top cause of cancer death, with a slight increase from 2020 [1,2]. The escalating mortality of lung cancer has become a global concern. Histologically, small cell lung cancer (SCLC) makes up 10%–15% of the total, while

non-small cell lung cancer (NSCLC) represents up to 85% of lung cancer diagnoses, and its predominant forms are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [1]. Despite therapeutic advances, the 5-year survival rate remains approximately 20%, largely due to late diagnosis, early recurrence, rapid resistance, heterogeneous therapeutic responses, and immune-related adverse events (irAEs) [3,4]. Immunotherapeutic drugs are being used comprehensively for those driven-gene mutation negative patients, nevertheless, only a fraction of them attain lasting benefit from immunotherapy, and biomarkers other than programmed death-ligand 1 (PD-L1) to predict response remain deficient. Emerging evidence suggests that the microbiota plays a part in tumor development across various cancer types [5]. Hence, gaining deeper insight into lung cancer pathophysiology and the lung microbiota's role might offer novel opportunities to improve clinical management and new drug development.

However, it was not until the mid-2000s, with advances in gene analysis techniques, that the presence of a low-biomass but diverse microbial community in the lower airways of healthy people was revealed. This delay was largely due to the scarcity of microorganisms in the lungs, combined with physiological and anatomical barriers that made sampling, isolation, and quantification difficult [6,7]. The respiratory microbiome comprises bacteria, viruses, fungi, and archaea, collectively termed the commensal microbiota [8]. Although its biomass is lower than that of other environmentally exposed organs like the gut and skin, the respiratory microbiota plays critical roles in lung health and disease, including lung cancers. Latest investigations have largely indicated direct modulation of the local immune landscape by the respiratory microbiota [9], with dysbiosis of the respiratory microbiota contributing to cancer development through induction of disordered inflammatory and immune responses [10]. Given that current evidence on viruses, fungi, and archaea remains limited and fragmented, this review focuses mainly on the bacterial microbiota, with only brief mention of other kingdoms where data are available.

Although the specific links between respiratory microbiota and lung cancer remain elusive, the broader relationship between them is being actively investigated. Increasing evidence has linked alterations in the airway and intratumor microbiome to lung cancer initiation, progression, and therapeutic response. Numerous microbiome populations implicated in lung cancer development have been identified, which may serve as novel diagnostic and therapeutic biomarkers and facilitate the advancement of personalized medicine [11]. Lung cancer patients usually exhibit reduced microbial diversity and enrichment of oral commensals such as *Veillonella* and *Streptococcus* [12,13]. Mechanistically, microbial metabolites reprogram host metabolism, suppress antitumor immunity, and drive angiogenesis [11,14,15]. Notably, the respiratory microbiome predicts PD-L1 expression and response to immune checkpoint inhibitors (ICIs), whereas antibiotic-induced dysbiosis is associated with worse clinical outcomes [16,17]. Patients treated with antibiotics before or during immunotherapy present with significantly lower progression-free survival and overall survival rates compared with patients who have not received antibiotics [18]. The respiratory microbiota and anticancer therapy engage in bidirectional interactions: the microbiota may enhance, impair, or mediate therapeutic efficacy, whereas cancer and its treatment concurrently reshape microbial composition. Elucidating this interplay is essential for optimizing therapeutic outcomes.

Although previous studies have investigated the relationship between the respiratory microbiota and lung cancer, our review provides novel insights into the compositional characteristics of the respiratory microbiome, its association with lung cancer, and the underlying mechanisms. We further summarize

the potential roles of the respiratory microbiome in lung cancer diagnosis, subtyping, staging, and treatment response prediction. Finally, through a critical evaluation of the limitations of current studies, we propose targeted future research directions concerning the respiratory microbiome, as well as optimization strategies for leveraging the respiratory microbiome in personalized precision therapy for lung cancer.

2. Respiratory microbiota and its alterations in lung cancer

2.1. The dynamic changes of the respiratory tract microbial community

The lungs are constantly exposed to microorganisms from the upper airways and inhaled air, yet conventional culture techniques rarely isolated bacteria from healthy lungs. Next-generation sequencing (NGS) has revealed a low-biomass (5–8.25 log copies/ml) bacterial community in the lower respiratory tract [18]. Although most of this microbial DNA derives from nonviable organisms (> 90% DNase I-sensitive) and approximately 33% of healthy lung samples are sterile [19,20], an increasing number of evidence supports the existence of a resident lung microbiota. Indeed, studies reported that viable bacteria in the respiratory tract can be cultured using optimized protocols [21,22]. Studies in animal models have demonstrated that bacterial load in the lungs increases during the first two weeks of life [23], and the stable development of the respiratory microbiota is shaped by birth mode, the first-hour environment, and exposures at 3–4 months of age [24]. It has been proposed that oral aspiration serves as a source of lower airway microbiota, and that the microbiomes of bronchoalveolar lavage (BAL) fluid are intermediate between those of saliva and lung tissue [25,26]. The abundance and composition of the respiratory microbiome are mainly regulated by the balance of these three factors: bacterial immigration, elimination, and replication [27]. This broad range of determinants drives continuous, low-magnitude turnover, implying time-contingent variation that complicates the study of the lung microbial system [28]. In humans, the respiratory microbiome exhibits a density gradient along the respiratory tract, with the highest load in the upper respiratory tract and the lowest in the lungs; its composition and function also differ significantly between the upper and lower airways, and the microbial community is in a dynamic state of constant turnover [10,29,30].

2.2. The composition and classification of the respiratory microbiota

The respiratory microbiome consists of bacteria, viruses, fungi and archaea [8], among which bacteria are the most abundant and best-studied. The bacterial component is primarily consists of bacteria from the phyla Bacteroidetes (e.g., *Prevotella*), Firmicutes (e.g., *Veillonella*, *Streptococcus*, *Megasphaera*, *Staphylococcus*), Proteobacteria (e.g., *Neisseria*, *Haemophilus*, *Sphingomonas*, *Pseudomonas*, *Acinetobacter*), Fusobacteria (e.g., *Fusobacterium*), and Actinobacteria (e.g., *Corynebacterium*) [10,18,31]. The core fungal community is dominated by the phyla Ascomycota, Basidiomycota, and Mucoromycota. At the genus level, *Aspergillus*, *Amorphotheca*, *Rhizophagus*, and *Malassezia* are present in notably high relative abundances [32]. Recent findings indicate that these microbial populations are critical for maintaining tissue homeostasis, and that their disruption contributes to the pathogenesis of diseases including asthma, chronic obstructive pulmonary disease (COPD), and lung cancer [18]. The homeostasis of the lung microbiota is influenced by multiple factors, including mode of delivery,

breastfeeding, disease status, lifestyle (notably diet), chronic infections, and antibiotic exposure. Maintenance of the pulmonary microbial ecosystem is essential for healthy lung homeostasis; disruption of this balance—referred to as dysbiosis—may alter tissue homeostasis and contribute to cancer development [23,33,34]. Segal *et al.* classified the lung microbiome into two distinct pneumotypes. The first, termed background predominant taxa (BPT) pneumotype, is characterized by low microbial biomass, whereas the second, designated supraglottic predominant taxa (SPT) pneumotype, exhibits a higher bacterial load and enrichment of oral microorganisms [35,36].

2.3. The characteristics of microbiota in lung cancer

Lung cancer patients exhibit significant alterations in the composition of the respiratory microbiota, characterized by reduced alpha diversity and enrichment of oral commensal [12,13,37–39]. These taxa, particularly *Veillonella*, promote lung carcinogenesis by activating pro-tumorigenic pathways (extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinase (PI3K), interleukin-17 (IL-17), vascular endothelial growth factor (VEGF)) and suppressing phosphatase and tensin homolog (PTEN), through mechanisms involving host inflammation, bacterial toxins, and carcinogenic metabolites [40]. Distinct microbial communities are associated with different histological subtypes, for example, lung adenocarcinoma is predominantly populated by *Acinetobacter*, *Propionibacterium*, *Staphylococcus*, and *Cyanobacteria*, whereas squamous cell carcinoma is enriched with *Enterobacter*, *Serratia*, and *Klebsiella* [41]. Certain taxa also correlate with clinical features. *Thermus* is more abundant in advanced-stage tumors, whereas *Legionella* is enriched in patients with metastasis [31,42]. Beyond bacteria, viral infections (Epstein–Barr virus (EBV), human papillomavirus (HPV), influenza, human immunodeficiency virus (HIV)) also contribute to lung cancer pathogenesis [43,44]. For instance, EBV manipulates host metabolism via latent membrane protein 1 (LMP1)/latent membrane protein 2A (LMP2A) [45], and HIV increases lung cancer risk with earlier onset [46]. Fungi represent another emerging player: *Blastomyces* is associated with lung cancer [47], and *Aspergillus sydowii* is enriched in lung adenocarcinoma, correlating with immunosuppression and poor outcome [48]. However, conflicting findings exist regarding the role of *Staphylococcus*: some studies suggest a protective role, while others report its DNA-damaging ability [49,50]. These discrepancies may arise from differences in the tumor microenvironment or from the diverse functions of distinct microbial species and strains. Nonetheless, the interactions between the respiratory microbiota and host defense responses are highly complex. Although lower respiratory tract microbiome analysis in the context of lung cancer remains at an early stage, with many questions unresolved, several studies have provided valuable insights (summarized in Table 1). Reported discrepancies may also arise from differences in lung cancer subtypes, sample types, sequencing methods, and choice of control specimens, underscoring the need to account for these factors when analyzing microbiome differences between cancerous and non-cancerous tissues.

Table 1. Review of microbiota found in patients with lung cancer.

Year	References	Analytical Method	Sample Type	Sample Size	Differential Findings
2024	Sun *et al.* [8]	Metagenomic sequencing	lung tissues	46	Actinobacteria, M. discipulorum
2021	Jang *et al.* [12]	16S rRNA gene sequencing, V3-V4	BALF	84	Veillonella dispar, Neisseria, Haemophilus
2021	Patnaik *et al.* [26]	16S rRNA gene sequencing, V3-V4	Saliva, BALF and lung tissues	48	Delftia, Staphylococcus, Sphingomonas, Psychromonas, and Serratia
2016	Yu *et al.* [31]	16S rRNA gene sequencing, V3-V4	lung tissues	165	Thermus and Legionella
2025	Yiminniyaze *et al.* [32]	metagenomic next-generation sequencing	lung tissues	50	Shewanella
2018	Tsay *et al.* [37]	16S rRNA gene sequencing, V4	bronchial brushing	39	Streptococcus, Veillonella
2019	Gomes *et al.* [38]	16S rRNA gene sequencing, V3 and V4-V6	BALF	103	Proteobacteria
2018	Apopa *et al.* [42]	16S rRNA gene sequencing, V1-V3	lung tissues	29	Cyanobacteria
2018	Liu *et al.* [49]	16S rRNA gene sequencing, V3-V4	bronchial brushing	42	Streptococcus and Neisseria
2018	Greathouse *et al.* [51]	16S rRNA gene sequencing, V1-V5	lung tissues	176	Acidovorax, Klebsiella, Rhodoferax, Anaerococcus
2026	Li *et al.* [52]	microbiological cultivation	sputum	724	Klebsiella, Candida albicans, Pseudomonas aeruginosa
2022	Zhang *et al.* [53]	Targeted Sequencing	lung tissues	53	Serratia marcescens, Actinomyces neesii, Enterobacter cloacae, and Haemophilus parainfluenzae
2023	Zhou *et al.* [54]	16S rRNA gene sequencing	lung tissues	43	Promicromonosporaceae and Chloroflexi
2015	Yan *et al.* [55]	16S rRNA gene sequencing	Saliva	20	Capnocytophaga, Selenomonas, and Veillonella
2022	Zeng *et al.* [56]	16S rRNA gene sequencing, V3-V4	BALF	46	Prevotella, Streptococcus, Veillonella, Neisseria, Actinomyces, Alloprevotella, and Porphyromonas
2021	Bello *et al.* [57]	16S rRNA gene sequencing, V3-V4	bronchial biopsies and saliva	25	Streptococcus, Rothia, Gemella and Lactobacillus
2024	Kim *et al.* [58]	16S rRNA gene sequencing, V3-V4	BALF	24	Chloroflexus, Neissera, and Veillonella
2025	Yang *et al.* [59]	16S rRNA gene sequencing	BALF	34	Cyanobacteria, Alloprevotella, Megasphaera, Saccharibacteria
2024	Wang *et al.* [60]	Metagenomic sequencing	BALF	21	L. acidophilus
2019	Huang *et al.* [61]	16S rRNA gene sequencing, V3-V4	BALF	40	Veillonell, Megasphaera, Actinomyces, Arthrobacter, Capnocytophaga, Rothia, Streptococcus, and Veillonella
2021	Dong *et al.* [62]	16S rRNA gene sequencing	lung tissues	143	Massilia, Phenylobacterium, Acidovorax and Pseudoxanthomonas

Table 1. *Cont.*

Year	References	Analytical Method	Sample Type	Sample Size	Differential Findings
2022	Huang *et al.* [63]	16S rRNA gene sequencing, V3-V4	sputum	85	Granulicatella, Actinobacillus, Actinomyces,Peptostreptococcus,Parvimonas, Pseudomona and Parvimonas
2021	Zheng *et al.* [64]	-	BALF	32	Lactobacillus rossiae, Burkholderia mallei and Bacteroides pyogenes
2025	Zhang *et al.* [65]	16S rRNA gene sequencing, V3-V4	BALF	26	Bacillus, Sphingomonas, Sediminibacterium
2026	Cavaliere *et al.* [66]	16S rRNA gene sequencing, V1-V3	Saliva	70	Actinomyces
2022	Chu *et al.* [67]	16S rRNA gene sequencing, V3-V4	BALF	46	Fusobacterium
2014	Hosgood *et al.* [68]	16S rRNA gene sequencing, V1-V2	Buccal and sputum	16	Granulicatella, Abiotrophia, and Streptococcus
2016	Lee *et al.* [69]	16S rRNA gene sequencing, V1-V3	BALF	28	Capnocytophaga, Selenomonas, and Veillonella
2017	Cameron *et al.* [70]	16S rRNA gene sequencing, V3-V4	Sputum samples	10	Streptococcus, Granulicatella adiacens, and Mycobacterium tuberculosis
2018	Liu *et al.* [71]	16S rRNA gene sequencing, V4	lung tissues	30	Streptococcus, Prevotella
2019	Jin *et al.* [72]	Metagenomics	BALF	91	Bradyrhizobium japonicum
2020	Cheng *et al.* [73]	16S rRNA gene sequencing, V3-V4	BALF	32	Capnocytophaga, Sediminibacterium, Gemmiger, Blautia and Oscillospira
2020	Druzhinin *et al.* [74]	16S rRNA gene sequencing, V3-V4	sputum	17	Haemophilus and Bergeyella
2022	Xia *et al.* [75]	16S rRNA gene sequencing	BALF	8	Neisseria, Megamonas, and Fusobacterium
2023	Zhang *et al.* [76]	Metagenomic sequencing	BALF	28	Campylobacter, Enterobacter, Debaryomyces, and Fusobacterium

3. Mechanisms of the respiratory microbiome on lung cancer pathogenesis

Although altered respiratory microbiota in the context of lung cancer has been described and may contribute to carcinogenesis, the mechanisms by which microbiota regulate tumor initiation and progression remain unknown. The respiratory microbiome may contribute to tumorigenesis either by directly acting on tumor cells or indirectly via modulation of the tumor-associated immunity. Evidence indicates that dysbiosis promotes malignancy through multiple mechanisms [51], including oncogene activation, metabolic regulation, chronic inflammation, and immune dysregulation within the lung tissue [18,41,77,78] (Figure 1).

3.1. Activation of oncogenes and pro-tumoral pathways

A primary mechanism by which respiratory microbiota promotes lung carcinogenesis involves direct interactions with lung cancer cells, including the activation of tumor-associated signaling pathways and the induction of host DNA damage [79,80]. Infected patients exhibit significantly higher tumor mutation burden (TMB) and increased frequency of copy number variations, particularly on chromosome 11 [52].

Furthermore, *Streptococcus intermedius* has been reported to shorten the cell cycle and inhibit apoptosis in lung cancer cells [81]. Tsay *et al.* demonstrated that lower airway dysbiosis, characterized by enrichment of Streptococcus and Veillonella, directly induces epithelial cell transformation *in vitro* and in a Kras- and Trp53-driven (KP) mouse model through activation of the PI3K and ERK pathways [37]. Intranasal lipopolysaccharide (LPS) promotes tumor growth through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) upregulation and Akt activation [82,83]. Gao *et al.* demonstrated that airway microbiota-derived D-phenylalanine, originating from *Metamycoplasma salivarium*, promotes lung cancer metastasis by inducing epithelial-mesenchymal transition (EMT) [84]. Apopa *et al.* showed that cyanobacteria-derived microcystins correlate with reduced CD36 expression and elevated levels of pro-tumorigenic poly (adenosine diphosphate ribose (ADP-ribose)) polymerase 1 (PARP1) in NSCLC [42,85,86], implicating CD36-mediated microbial ligand processing in lung carcinogenesis. Although certain microbial taxa have been linked to specific driver mutations, including *TP53* and *EGFR* [51,52], the intrinsic mechanisms underlying these associations remain to be elucidated.

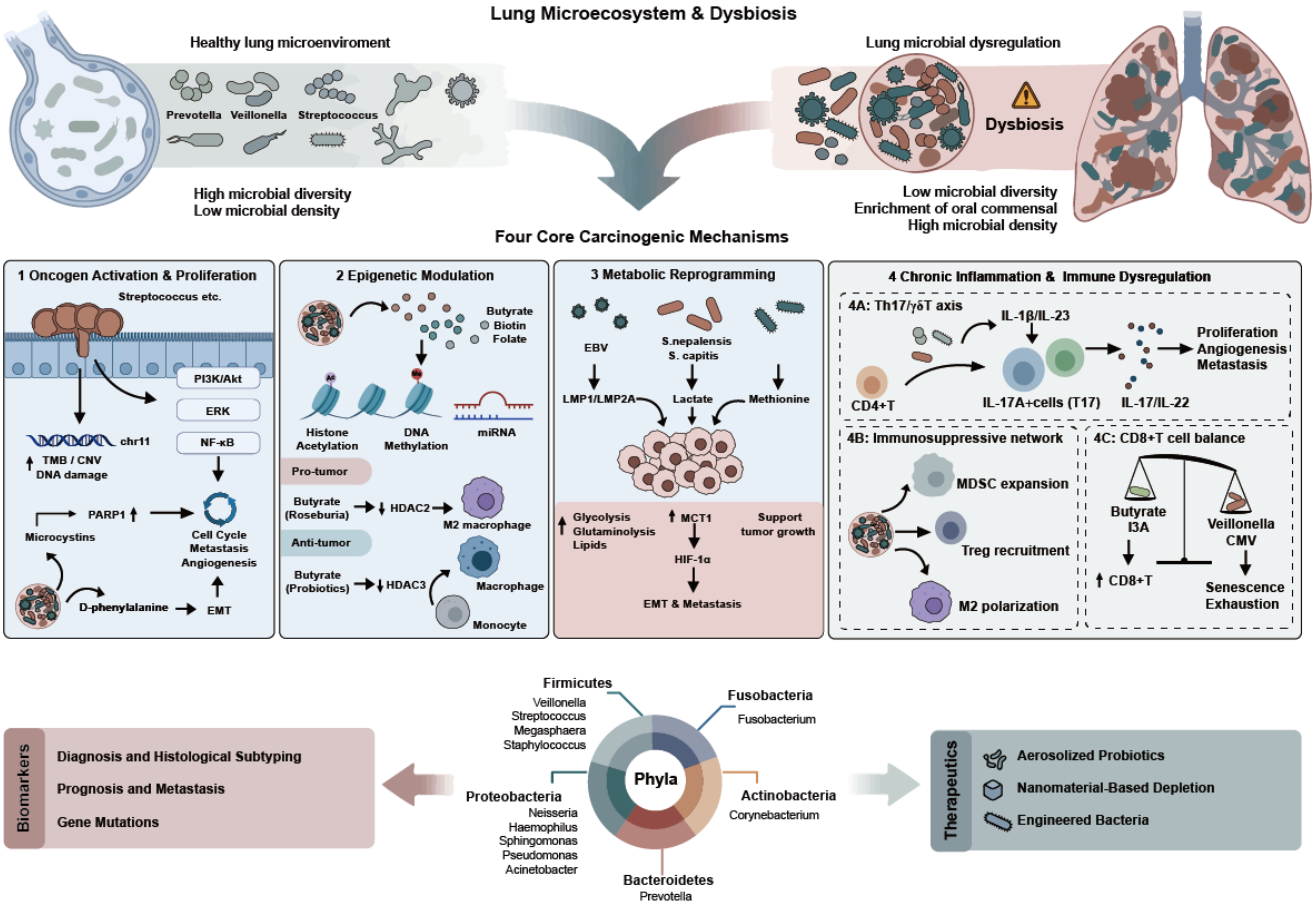

Figure 1. The respiratory microbiota in lung cancer: composition, mechanistic roles, and clinical translation. The upper panel depicts the composition of the healthy lung microbiota and the shift toward dysbiosis in lung cancer. The middle panel illustrates four interconnected mechanistic pathways by which dysbiosis promotes lung tumorigenesis: oncogenic signaling/DNA damage, epigenetic modulation, metabolic reprogramming, and chronic immune dysregulation. The lower panel summarizes the clinical applications of microbial signatures as diagnostic/prognostic biomarkers and emerging microbiota-targeted therapeutic strategies.

3.2. Epigenetic modulation induced by microbial metabolites

Microbial metabolites exhibit dual regulatory roles in epigenetic modulation. Metabolites such as butyrate, biotin, and folate modulate host epigenetic processes, including histone acetylation, deacetylation, biotinylation, and DNA methylation [41]. For instance, butyrate-producing bacteria such as *Roseburia* promote metastasis by inhibiting histone deacetylase 2 (HDAC2) via butyrate, which increases histone H3 lysine 27 (H3K27) acetylation at the H19 promoter and upregulates the long non-coding RNA (lncRNA) H19, thereby inducing M2-like macrophage polarization [14]. Conversely, butyrate derived from gut probiotics modulates miRNA expression in NSCLC A549 cells to suppress proliferation and inhibits histone deacetylase 3 (HDAC3) to drive monocyte-to-macrophage differentiation, reducing inflammatory mediators and enhancing antimicrobial activity [87]. These findings suggest that the effects of butyrate on lung cancer are bidirectional, depending on its microbial origin and the specific epigenetic targets involved.

3.3. Microbial metabolites regulate tumor performance

Microbial and viral factors reprogram host cell metabolism to promote lung cancer progression. EBV infection, implicated in a subset of lung cancers, modulates cellular metabolism through latent membrane proteins LMP1 and LMP2A, enhancing glycolysis, glutaminolysis, and lipid metabolism to support viral replication and facilitate immune evasion within the tumor microenvironment [45]. Among bacterial-derived metabolites, lactate secreted by *Staphylococcus nepalensis* and *S. capitis* upregulates monocarboxylate transporter 1 (MCT1) on lung cancer cells, facilitating lactate uptake and activating hypoxia-inducible factor (HIF)-1α signaling, which drives EMT and metastasis; this effect is reversed by bacterial lactate gene knockout or MCT1 inhibition [15]. Furthermore, airway microbiota-derived D-phenylalanine promotes NSCLC cell proliferation, migration, and invasion by inducing EMT, thereby enhancing lung cancer metastasis [84]. In addition, the lung tumor microbiota can supply essential nutrients such as methionine to cancer cells in a bidirectional exchange, suggesting cooperative metabolic crosstalk that supports tumor growth under nutrient-restricted conditions [88]. Microbial metabolites are emerging as potential regulators of anti-tumor immune responses [89]. Moreover, manipulating microbial communities in the TME could reshape the metabolic landscape, offering new therapeutic opportunities for lung cancer.

3.4. Chronic inflammation and tumor immune dysregulation

Although the specific relationship among respiratory microbiota, immune regulation, and lung cancer remains unclear, studies have demonstrated that microbiota-immune crosstalk plays a critical role in driving inflammation and lung tumorigenesis [9].

3.4.1. Th17 and γδ T cell-mediated inflammation

Respiratory microbiota dysbiosis directly drives tumorigenesis by inducing T helper 17 (Th17)/γδ T cell-mediated inflammatory responses. The SPT pneumotype has been shown to correlate with a Th17 cell-related lung inflammation [36], which has been identified as an important factor in the progression and metastasis of lung cancer [90]. IL-17 secreted by these cells perpetuates chronic inflammation and

accelerates malignant progression. Segal *et al.* reported that enrichment of oral bacteria such as *Prevotella*, *Rothia*, and *Veillonella* in the lung correlates with elevated Th17-associated cytokines (IL-1α, IL-1β, IL-6, fractalkine, IL-17) and enhanced recruitment of Th17 cells and neutrophils [36]. Th17 cells secrete IL-17 and IL-22 to drive tumor growth, angiogenesis, metastasis, and pro-survival signaling through VEGF/VEGF-C (for IL-17) and STAT3 (for IL-22) [90]. Stone *et al.* demonstrated that *Acidovorax temperans* accelerates lung tumor development by polarizing $CD4^+$ T cells into an $IL\text{-}17A^+$ phenotype detectable in $CD4^+$ and γδ T cell populations (T17). These T17 cells share a common gene expression program predictive of poor survival in human lung adenocarcinoma (LUAD) [91]. Jin *et al.* showed that lung commensal bacteria trigger Myd88-dependent IL-1β/IL-23 production, inducing $V\gamma6^+V\delta1^+$ γδ T cells to secrete IL-17 and drive lung adenocarcinoma [9]. Indeed, in a K-ras-driven mouse model, IL-17 promotes lung tumorigenesis by enhancing tumor cell proliferation, angiogenesis, and recruitment of pro-tumor myeloid cells; these effects are diminished in the absence of IL-17 [92].

3.4.2. MDSC, Treg and macrophage-mediated immunosuppression

Beyond Th17 cells, the respiratory microbiota orchestrates broader immunosuppressive networks involving myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor-associated macrophages (TAMs). For instance, *Aspergillus sydowii* promotes tumor progression through β-glucan/Dectin-1/caspase recruitment domain-containing protein 9 (CARD9) signaling, which triggers IL-1β-dependent MDSC expansion. These MDSCs suppress $CD8^+$ T cell cytotoxicity and increase the frequency of $PD\text{-}1^+$ $CD8^+$ T cells, thereby establishing an immunosuppressive microenvironment [48]. Beyond MDSCs, exposure of the lower airways to oral commensals induces inflammatory cytokines and upregulates PD-L1 on T cells while promoting Treg recruitment [93]. Additionally, microbial metabolites such as butyrate, which promotes metastasis via the H19 pathway, also enhance MDSC and Treg immunosuppressive functions [94]. Regarding macrophage-mediated immunosuppression, *Talaromyces marneffei*, a fungus enriched in NSCLC patients, promotes tumor growth by inducing dose-dependent M2 macrophage polarization through activation of the arginine-ornithine cycle; inhibition of arginase reduces both M2 polarization and fungal survival [95].

3.4.3. $CD8^+$ T cell modulation and antitumor immunity

In contrast to the predominantly inhibitory effects described above, certain microbial metabolites and early-life microbial exposures can positively regulate $CD8^+$ T cell-mediated antitumor immunity. For example, butyrate directly enhances anti-PD-1 efficacy by amplifying $CD8^+$ T cell receptor signaling [96]. Similarly, probiotic-derived indole-3-aldehyde (I3A), an agonist of the aryl hydrocarbon receptor (AhR), activates the AhR signaling pathway in tumor-infiltrating $CD8^+$ T cells, thereby further potentiating antitumor immunity [97]. However, under different microbial conditions, the same immune cell subset may undergo functional impairment. Dysbiosis of *Veillonella parvula* upregulates PD-1 expression on $CD8^+$ T cells, contributing to their exhaustion [13]. Moreover, cytomegalovirus (CMV) drives the accumulation of senescence-associated $CD8^+$ T cells (T8sen), which correlates with resistance to immunotherapy in advanced NSCLC [98]. Collectively, the net outcome of microbiota-immune crosstalk on $CD8^+$ T cells is highly context-dependent, ranging from reinvigoration to exhaustion and

senescence. The direction of this effect is determined by the specific microbial species, metabolites, and timing of exposure.

The four mechanistic axes described above do not function in isolation but rather converge into an integrated regulatory network. Butyrate exemplifies this interconnectivity: depending on its microbial origin and local tumor microenvironment, it can promote metastasis via the HDAC2/H19/M2 polarization axis [14], enhance anti-PD-1 efficacy through $CD8^+$ T cell signaling [96], or reinforce MDSC/Treg-mediated suppression [94]. Beyond metabolite signaling, epigenetic alterations modulate both oncogene expression and immune cell fate [9,79,80]; chronic inflammation reshapes the tumor metabolome and microbial niches [9]; and metabolic reprogramming of cancer cells reciprocally influences local immunity [88]. Recognizing these cross-regulatory relationships not only deepens our understanding of lung cancer pathogenesis but also reveals therapeutic opportunities for intervention. Indeed, in a melanoma model, localized antibiotic treatment combined with inhaled aerosolized *Lactobacillus rhamnosus* reduced IL-10-producing Tregs and enhanced anti-tumoral NK and T cell activation, thereby alleviating immune suppression within the tumor microenvironment and decreasing lung metastasis of B16 melanoma [99]. This example demonstrates that the lung microbiota is modifiable and that such modulation can profoundly influence antitumor immunity. Thus, integrating mechanistic insights with proof-of-concept interventions is essential for translating microbiome knowledge into effective diagnostic and therapeutic strategies for lung cancer.

4. The respiratory microbiome as a diagnostic predictor of lung cancer

Respiratory microbiota signatures play a critical role in predicting lung cancer development, histological subtypes, cancer stages and gene mutations, thereby facilitating clinical diagnosis.

4.1. Respiratory microbiota signatures predict lung cancer pathogenesis

Emerging evidence indicates that specific respiratory microbiota signatures may serve as biomarkers for lung cancer risk and early diagnosis [100]. Certain compositional shifts have been associated with increased risk, including higher abundance of *Haemophilus*, *Enterobacter*, *Actinomyces*, *Promicromonosporaceae*, *Chloroflexi Streptococcus*, *Granulicatella*, and *Leptotrichia* [53,54,100]. A panel of lung microbial taxa—comprising *Streptococcus, Veillonella, Neisseria, Megasphaera, Capnocytophaga*, *and Prevotella* (as summarized in Table 2)—is consistently enriched in lung cancer patients, suggesting their potential as non-invasive diagnostic biomarkers [55–58]. The auxiliary diagnostic value of respiratory microbiota signatures has been further corroborated by multiple studies using diverse sample types. A microbial classifier validated in 400 individuals accurately predicted lung cancer prior to clinical diagnosis [101]. Furthermore, the presence of *Enterococcus*, *Capnocytophaga*, or *Actinomyces* in lower airway samples identified malignancy with 70% accuracy, whereas *Microbispora* indicated benign disease [102]. In bronchoalveolar lavage fluid (BALF), the combination of *Megasphaera* and *Saccharibacteria* distinguished benign from malignant pulmonary nodules (AUC = 0.882) [59]. Additionally, Zhang *et al.* reported that *Lactobacillus acidophilus* abundance combined with body mass index (BMI) predicted lung cancer risk with an AUC of 0.985 [60]. Similarly, in bronchial biopsies, *Streptococcus* abundance differentiated lung cancer patients from controls with an AUC of 0.897 [57]. Notably, a machine learning model based on archaeal signatures distinguished lung

cancer patients from healthy controls with 99% accuracy [103]. Collectively, these studies, spanning different sampling approaches, underscore the potential of lung microbiome profiling for early detection; however, standardized multicenter trials are urgently required to validate their predictive value.

Table 2. Lung microbiome and their association with lung cancer.

Microbial taxa	Analytical Method	Sample Type	Correlation with Lung Cancer	Potential mechanisms in lung cancer
M. discipulorum [8]	Metagenomic sequencing	lung tissues	Enriched in the lung tissue of patients with ES-LUAD	N.D.
Acinetobacter [8,32,38]	16S rDNA sequencing and mNGS	BALF and lung tissue	Enriched in lung cancer and LUAD [38]	N.D.
Neisseria [12,49,55,56,58,75]	16S rDNA sequencing	bronchial brushing and BALF	Conflicting reports exist: decreased in lung cancer BALF [55] *versus* abundant in BALF and tissue [49,56,58,75]; more in the low-PD-L1 group [12]	N.D.
Veillonella [12,37,55,56,58,61,69]	16S rDNA sequencing	Saliva, bronchial brushing and BALF	Enriched in lung cancer [58], associated with LUAD [61] and advanced disease [13]; promotes LLC tumor growth *in vivo* [56] and was dominant in the high-PD-L1 group [12]	Upregulate ERK and PI3K pathway [37], positively correlated with Th17 cells and neutrophils [36]
Prevotella [13,56,71]	16S rDNA sequencing	Lung tissues and BALF	Enriched in lung cancer, associated with more advanced disease [13]	Upregulate ERK and PI3K pathway [37], positively correlated with Th17 cells and neutrophils [36]
Delftia [26]	16S rDNA sequencing	Saliva	More prevalent in recurrence patients	N.D.
Sphingomonas [26,38]	16S rDNA sequencing	BALF and lung tissues	Enriched in lung cancer/LUAD and increased in the recurrence group [26]	Positively correlated with macrophage abundance and IFN-γ level in the BAL [36]
Staphylococcus [26,38,49]	16S rDNA sequencing	BALF and lung tissues	Enriched in BALF of LUAD [38] and had a significantly greater abundance in the tissues of recurrence group [26]	N.D.
Thermus [31]	16S rDNA sequencing	lung tissues	Enriched in advanced-stage (IIIB/IV) lung cancer patients	N.D.
Legionella [31]	16S rDNA sequencing	lung tissues	Enriched in metastatic lung cancer patients	N.D.
Pseudomonas [31,38,51,63]	16S rDNA sequencing	Lung tissues, BALF and sputum	Enriched in LUAD [51], and positively associated with lymph node metastasis [63]	Positively correlated with macrophage abundance and IFN-γ level in the BAL [36], neutrophil elastase activity [104] and L-valine biosynthesis [63]
Enterobacter [32,38,76]	16S rDNA and Metagenomicsequencing	BALF and lung tissue	Enriched in lung cancer/LUSC [38] and correlates with worse survival [32]	N.D.
Rothia [36,57,61]	16S rDNA sequencing	BALF and saliva	Enriched in LUSC [36] and central lung cancer [57]	Positive associated with elevated levels of various Th17 cytokines [36]

Table 2. *Cont.*

Microbial taxa	Analytical Method	Sample Type	Correlation with Lung Cancer	Potential mechanisms in lung cancer
Streptococcus [37,56,57,61,68,70,71]	16S rDNA sequencing	Lung tissues, BALF, bronchial biopsies and saliva	Enriched in lung cancer, LUAD [38] and associated with more advanced disease [13]	Upregulate ERK/PI3K [37], correlates negatively with neutrophil elastase [104], promotes metastasis through pseudohypoxia [15], and accelerates cell cycle while blocking apoptosis in lung cancer cells [81]
Brevundimonas [38]	16S rDNA sequencing	BALF	Enriched in LUAD	N.D.
Propionibacterium [38]	16S rDNA sequencing	BALF	Enriched in LUAD	N.D.
Actinobacillus [38]	16S rDNA sequencing	BALF	Enriched in LUSC	N.D.
Phenylobacterium [38,62]	16S rDNA sequencing	BALF and lung tissue	Enriched in lung cancer and LUAD [38]	N.D.
Rhodoferax [51]	16S rDNA sequencing	lung tissues	Enriched in LUSC	N.D.
Klebsiella [51,52]	16S rDNA sequencing	lung tissues	Enriched in LUSC and associated with cases carrying *TP53* mutations [52]	N.D.
Acidovorax [51,62]	16S rDNA sequencing	lung tissues	Enriched in LUSC with *TP53* mutations	Induce a pro-tumorigenic neutrophil phenotype and promoting the polarization of IL-17A$^+$ Th17 cells [91]
Promicromonosporaceae [54]	16S rDNA sequencing	lung tissues	Enriched in lung cancer tissue	N.D.
Chloroflexus [54,58]	16S rDNA sequencing	lung tissues and BALF	Enriched in lung cancer [54,58]	N.D.
Selenomonas [55]	16S rDNA sequencing	Saliva	Enriched in lung cancer	N.D.
Capnocytophaga [55,73]	16S rDNA sequencing	Saliva	Enriched in lung cancer and LUSC	N.D.
Porphyromonas [56]	16S rDNA sequencing	BALF	Enriched in lung cancer	N.D.
Alloprevotella [56,59]	16S rDNA sequencing	BALF	Enriched in the NSCLC	Correlated with high-frequency chromosomal aberrations in lung cancer [74] and better response to chemotherapy combined with immunotherapy [59]
Cyanobacteria [42,59]	16S rDNA sequencing	lung tissues	Enriched in LUAD [42]	Cyanobacteria-derived microcystin reduces CD36 and elevates PARP1, promoting inflammation-associated lung carcinogenesis [42]
Megasphaera [61]	16S rDNA sequencing	BALF	Enriched in LUAD	N.D.

Table 2. *Cont.*

Microbial taxa	Analytical Method	Sample Type	Correlation with Lung Cancer	Potential mechanisms in lung cancer
Arthrobacter [61]	16S rDNA sequencing	BALF	Enriched in LUAD	N.D.
Actinomyces [61,63,66]	16S rDNA sequencing	BALF and sputum	Enriched in LUAD [61]/advanced-stage (IIIB/IV) [63] and independently associated with poorer ICI outcomes in NSCLC [66]	N.D.
Massilia [62]	16S rDNA sequencing	lung tissues	Enriched in *TP53*-mutated lung tumor, more abundant in smoker	Degrade phenanthrene, eliminating PAH-induced DNA damage
Sphingobacterium [62,65]	16S rDNA sequencing	lung tissues	Enriched in lung tumor tissues of smokers and embrace progression after ICIs	Degrade phenanthrene, eliminating PAH-induced DNA damage [62], and remodulate lipid and essential amino acid degradations [65]
Pseudoxanthomonas [62]	16S rDNA sequencing	lung tissues	Abundant in lung tumor tissue	N.D.
Parvimonas [63]	16S rDNA sequencing	Sputum	Positively associated with lymph node metastasis in NSCLC and enriched in patients with *EGFR* mutation	N.D.
Actinobacillus [63]	16S rDNA sequencing	Sputum	Enriched in stages I-II lung cancer patients	N.D.
Peptostreptococcus [63]	16S rDNA sequencing	Sputum	Associated with intrathoracic metastasis	Associated with incomplete reductive TCA cycle
Granulicatella [63,68,70]	16S rDNA sequencing	Sputum	Enriched in lung cancer patients, significantly in stages I-II [63]	N.D.
Bacillus [65]	16S rDNA sequencing	BALF	Associated with positive responses to ICI interventions	N.D.
Sediminibacterium [65,73]	16S rDNA sequencing	BALF	Enriched in lung cancer and embrace progression after ICIs	Liable to remodulate lipid and essential amino acid degradations [65]
Fusobacterium [67,75,76]	16S rDNA and Metagenomic sequencing	BALF	Enriched in lung cancer and associated with a poor response to anti-PD-1 therapy [67]	N.D.
Abiotrophia [68]	16S rDNA sequencing	Sputum	Enriched in never-smoking lung cancer patients	N.D.
Mycobacterium tuberculosis [70,105]	16S rDNA sequencing	Sputum	Increases the risk of lung cancer [105]	Induce chronic inflammation, oxidative stress, EMT, and immune checkpoint dysregulation [106]
Bradyrhizobium japonicum [72]	Metagenomics	BALF	Enriched in in patients with lung cancer	N.D.
Gemmiger [73]	16S rDNA sequencing	BALF	Enriched in lung cancer	N.D.
Blautia [73]	16S rDNA sequencing	BALF	Enriched in lung cancer	N.D.
Oscillospira [73]	16S rDNA sequencing	BALF	Enriched in lung cancer	N.D.
Haemophilus [74]	16S rDNA sequencing	Sputum	Enriched in lung cancer	N.D.

Table 2. *Cont.*

Microbial taxa	Analytical Method	Sample Type	Correlation with Lung Cancer	Potential mechanisms in lung cancer
Bergeyella [74]	16S rDNA sequencing	Sputum	Enriched in lung cancer	N.D.
Megamonas [75]	16S rDNA sequencing	BALF	Enriched in lung cancer	N.D.
Campylobacter [76]	Metagenomic sequencing	BALF	Enriched in tumor-burden lung segments	N.D.
Debaryomyces [76]	Metagenomic sequencing	BALF	Enriched in tumor-burden lung segments	Reduce $CD8^+$ T cells [107]

4.2. Respiratory microbiota signatures predict lung cancer histological subtypes

The composition of the respiratory microbiota differs across lung cancer subtypes. For example, Cyanobacteria predominates in BALF from patients with NSCLC compared to those with SCLC, suggesting a potential microbial distinction between these two major histological types [59]. Further compositional differences have been observed between LUAD and lung squamous cell carcinoma (LUSC). Greathouse *et al.* reported that *Acidovorax*, *Klebsiella*, *Rhodoferax*, and *Anaerococcus* are more abundant in LUSC cases with *TP53* mutations, an association not observed in LUAD [51]. Gomes *et al.* found that *Brevundimonas*, *Acinetobacter*, and *Propionibacterium* were enriched in LUAD, whereas *Enterobacter* was relatively more enriched in LUSC [38]. Huang *et al.* observed significantly higher levels of *Veillonella*, *Megasphaera*, *Actinomyces*, and *Arthrobacter* in LUAD than in LUSC, while *Capnocytophaga* and *Rothia* were lower in LUAD [61]. Additionally, *Brevundimonas*, *Ruminococcus*, and *Polaromonas* have been identified as differentially abundant taxa between LUAD and LUSC, and the fungal genus *Blastomyces* is increased in patients with LUSC [47,51,62]. Collectively, these findings indicate that distinct bacterial signatures may assist in histological subtyping of lung cancer, although current microbiome-based diagnostic models lack sufficient specificity and sensitivity.

4.3. Respiratory microbiota signatures predict lung cancer stages and gene mutations

Respiratory microbial signatures also correlate with lung cancer stages and gene mutations. In patients with NSCLC, *Veillonella*, *Prevotella*, *Streptococcus*, *Thermus*, and *Actinomyces* are more strongly associated with advanced stages (III–IV), whereas *Flavobacterium*, *Granulicatella*, and *Actinobacillus* are associated with earlier stages (I–II) [13,31,63]. *TP53* mutations represent the most frequently co-occurring genetic alterations alongside microbial infections [52]. The genera *Acidovorax*, *Klebsiella*, *Rhodoferax*, *Comamonas*, and *Polaromonas* have been reported to be strongly associated with *TP53* mutations [51,52]. However, it has also been suggested that *TP53* mutations themselves may drive alterations in the tumor microbiota [108], rendering the relationship between microbial changes and *TP53* status more complex and challenging to attribute to causality. In contrast, *EGFR* mutations are commonly found in patients without microbial infections [52]; the genus *Parvimonas* is enriched in patients with *EGFR*-mutant LUAD [63], whereas *Candida albicans* and *Pseudomonas aeruginosa* are detected exclusively in cases harboring *EGFR* mutations [52]. Additionally, the abundance of *Rhizopus oryzae, Natronolimnobius innermongolicus*, and *Staphylococcus sciuri* in bronchoscopy samples positively correlates with *EGFR* expression levels in cancer cells [64]. Collectively, these recent studies

(summarized in Table 2) suggest that the respiratory microbiome may soon become a critical diagnostic and preventive biomarker for lung cancer status, histological subtype, tumor stage, and gene mutations. Nevertheless, this predictive value remains to be validated in large-scale, multicenter clinical trials, and the intrinsic mechanisms linking the microbiome to these clinical parameters warrant further investigation.

5. Respiratory microbiota as therapeutic and prognostic predictors of lung cancer

5.1. Respiratory microbiota as a therapeutic predictor of ICI response in lung cancer

Although PD-L1 expression serves as the primary clinical predictor of efficacy for ICIs, tumor heterogeneity and interindividual variability often limit the predictive accuracy of PD-L1 alone, underscoring the need for additional biomarkers, such as respiratory microbial signatures [109]. The influence of the microbiota on cancer treatment outcomes has been well documented in melanoma and hematological malignancies; however, the role of the pulmonary microbiota in lung cancer therapy remains underexplored, as most existing research has focused on the gut microbiota [110]. Despite limited direct evidence, emerging data indicate that the respiratory microbiota may modulate antitumor immune responses and thereby affect ICI efficacy [94,65]. Notably, patients receiving antibiotic therapy before or during immunotherapy exhibit significantly poorer survival, highlighting the adverse impact of dysbiosis on treatment outcomes [17,111]. In a study of 70 patients with stage IV NSCLC receiving anti-PD-1/PD-L1 monotherapy, a salivary microbiome signature characterized by high abundance of *Actinomyces* was independently associated with inferior ICI outcomes [66]. Another prospective study involving 84 patients with NSCLC reported that *Veillonella dispar* predominated in the high PD-L1 expression group (≥ 10%) and among immunotherapy responders, whereas *Haemophilus influenzae* and *Neisseria perflava* were dominant in non-responders, and *Neisseria* species were more abundant in the low PD-L1 group [12]. Furthermore, Zapata *et al.* identified *Gemella* and *Bacteroidota* abundance in the respiratory microbiota as a potential predictor of ICI resistance, while *Lachnoanaerobaculum* and *Bacillus* abundance emerged as a candidate biomarker for favorable ICI response [65,112]. Intratumoral microbial heterogeneity in lung cancer, particularly enrichment of *Fusobacterium*, has also been linked to immunotherapy resistance [67]. Additionally, the presence of specific microbial metabolites in plasma and the profile of volatile organic compounds (VOCs) in exhaled breath have been associated with response to anti-PD-1 therapy [113–117]. The presence of *Alloprevotella* in BALF has been associated with improved response to combined chemotherapy and immunotherapy [59].

5.2. Respiratory microbiota as a predictor of irAEs in lung cancer immunotherapy

Approximately 40% of lung cancer patients receiving ICIs develop immune-related adverse events (irAEs), underscoring the need for early predictive biomarkers. Chau *et al.* reported that reduced gut alpha diversity was correlated with both treatment response and irAEs [118], and additional studies have suggested that modulation of the gut microbiota may mitigate irAEs in patients with NSCLC [119]. However, the association between the respiratory microbiota and irAEs has not yet been investigated. Future prospective studies and mechanistic investigations are warranted to validate these candidate biomarkers and to explore microbiota-targeted interventions aimed at optimizing immunotherapy and reducing the incidence of irAEs.

Microbial status has been reported to influence outcomes of targeted therapy. Lung cancers harboring *EGFR* mutations in the absence of concurrent microbial infections were associated with a higher objective response rate to *EGFR* tyrosine kinase inhibitors (TKIs) and with improved survival [52]. Nevertheless, no studies to date have reported an association between the respiratory microbiota and response to radiotherapy in lung cancer.

5.3. Respiratory microbiota as prognosis predictors of lung cancer

5.3.1. Respiratory microbiota predicts short survival in lung cancer

Accumulating evidence has established associations between specific respiratory microbiota and poor prognosis in lung cancer [120]. The operational taxonomic units (OTUs) of *Streptococcus*, *Rothia*, *Veillonella*, and *Prevotella* are frequently associated with poor prognosis and tumor progression in lung cancer [13]. A compositional shift from Proteobacteria to Firmicutes has also been implicated in lung cancer progression [39]. Zeng *et al.* demonstrated that *Veillonella* promotes lung cancer progression *in vivo*, potentially via metabolic pathways involving ribosome function, secondary metabolite biosynthesis, and pyrimidine metabolism [56]. In lung cancer, decreased relapse-free survival is associated with increased abundance of the classes *Bacteroidia* and *Clostridia* and the orders *Bacteroidales* and *Clostridiales* in tissue; conversely, increased relapse-free survival is associated with increased abundance of the classes *Alphaproteobacteria* and *Betaproteobacteria* and the orders *Burkholderiales* and *Neisseriales* [77]. Furthermore, Zhang *et al.* reported that a panel of four bacterial taxa (*Haemophilus parainfluenzae*, *Serratia marcescens*, *Acinetobacter junii*, and *Streptococcus constellatus*) predicted two-year survival with 90.7% accuracy, further underscoring the prognostic potential of respiratory microbial signatures [53]. Moreover, in LUSC, lower tumor bacterial richness and a gene-microbe multimodal model (area under the curve [AUC] = 0.81) predicted recurrence and metastasis risk. The risk score was significantly and inversely correlated with patient survival, including overall survival, progression-free interval, disease-specific survival, and disease-free interval, and host-microbe interactions were more prominent in LUSC than in LUAD [121].

5.3.2. Respiratory microbiota predicts metastasis status in lung cancer

Several microbial signatures have been associated with metastasis. Yu *et al.* reported that *Legionella* abundance is higher in lung cancer patients who develop metastases [31], and that airway microbiota-derived D-phenylalanine serves as a predictor of NSCLC metastasis, with elevated BALF levels indicating a high risk of metastasis [84]. In LUAD, the phylum *Firmicutes* and the genus *Streptococcus* are significantly more abundant in patients without distant metastasis, and *Streptococcus* can predict distant metastasis. In LUSC patients, the genera *Veillonella* and *Rothia* are significantly elevated in those with distant metastasis, suggesting their potential as predictive biomarkers for metastasis in this subtype [61]. Additionally, intrathoracic metastasis is associated with increased *Peptostreptococcus*, while lymph node metastasis correlates with *Parvimonas* and *Pseudomonas* [63].

Collectively, these findings indicate that respiratory microbial signatures—detectable in saliva, BALF, and tumor tissue—hold promise as non-invasive or minimally invasive biomarkers for predicting lung cancer

progression, metastasis, recurrence, and overall prognosis. However, the underlying mechanisms remain to be fully elucidated, and prospective validation is required prior to clinical translation.

6. Therapeutic targeting of the respiratory microbiota in lung cancer

The microbiota has emerged as an actionable target for lung cancer therapy [122]. Modulation of microbial communities may enhance treatment efficacy—for instance, by boosting immunotherapy responses while mitigating therapy-related dysbiosis [123,124]. To date, most microbiota-directed research has focused on the gut, where probiotics, specific bacterial taxa, and fecal microbiota transplantation have demonstrated preclinical benefits in lung cancer models [123,125]. In contrast, strategies that directly target the respiratory microbiota remain nascent. Recent advances have explored three distinct approaches: aerosolized probiotics, nanomaterial-based microbial depletion, and engineered bacterial systems [4]. Each offers unique mechanisms to reshape the lung tumor microenvironment.

6.1. Aerosolized probiotics

Probiotics play a crucial role in maintaining respiratory microbial homeostasis through immunomodulation, antimutagenic and anticarcinogenic activities, and pathogen suppression, with strain-specific effects [126]. The lung offers unique advantages for drug delivery (high permeability, large surface area, low proteolytic activity, and avoidance of first-pass metabolism), making nebulizers and inhalers effective for delivering probiotics to enhance NK/T cells, antigen-presenting cells, and type-1 interferons while regulating cytokines to prevent cytokine storm [127]. However, research on the preventive or therapeutic application of these approaches in lung cancer remains limited. Aerosolized probiotics can reverse pulmonary immunosuppression via microbial community restoration and immune tolerance modulation [128]. Indeed, inhalation of NSCLC patient-derived lung microbiota in mice reshapes the microbiome (*Pasteurella* replacing *Delftia*) and suppresses lung cancer cell proliferation [129]. Aerosolized *Lactobacillus rhamnosus* GG (*GG, derived from the initials of Goldin and Gorbach*) or *Bifidobacterium* have been shown to reshape the lung immunosuppressive microenvironment and enhance antitumor efficacy [99,130]. More recently, *Paenibacillus odorifer*, enriched in healthy individuals, was identified as a candidate probiotic in the lower respiratory tract. It correlates with the production of the antitumor metabolite acetate and suppresses lung cancer cell proliferation in time- and dose-dependent manners *in vivo* [131]. These findings suggest that *P. odorifer* may serve as a novel probiotic agent for lung cancer prevention or treatment, warranting further *in vivo* validation and clinical exploration. Despite promising results, studies on pulmonary probiotic delivery remain scarce. Future research should optimize aerodynamic particle size (1–5 μm) for lung deposition while avoiding disruption of resident microbiota or disease induction. Careful risk-benefit and strain-specific safety evaluation is essential before clinical translation.

6.2. Nanomaterial-based strategies

Nanotechnology provides innovative tools for the direct elimination of pathogenic microbes or the repurposing of bacterial components to enable targeted drug delivery, thereby overcoming chemoresistance and enhancing antitumor immunity. A recent study developed an inhalable metal-organic network that disrupts bacterial iron respiration, inhibiting microbe-induced drug inactivation and suppressing tumor growth in lung cancer models [132]. Beyond direct microbial elimination, probiotic-derived nanomaterials

offer precision targeting. Bifidobacterium infantis serves as a pre-implanted carrier to recruit nano-drugs to hypoxic lung tumor regions, improving bioavailability and reducing toxicity [133,134]. Metabolite-driven nanosynthesis also shows selective antitumor activity: gold nanoparticles from Lactobacillus acidophilus metabolites target A549 cells without harming normal cells [135], and exopolysaccharide-coated selenium nanoparticles exhibit anti-lung cancer effects [136]. Collectively, these examples illustrate how nanotechnology harnesses probiotic components for selective cytotoxicity, drug delivery, and immune modulation, offering a versatile strategy for lung cancer therapy. Nevertheless, further basic and clinical studies are urgently needed to validate these approaches and translate them into clinical practice.

6.3. Engineered bacteria

Engineered bacterial systems have emerged as a promising platform for lung cancer therapy. Two main strategies exist: engineering bacterial OMVs and developing programmable live bacteria [4]. This platform offers three key advantages: coordinated innate/adaptive immunity with reduced off-target toxicity, tumor-specific colonization via bacterial immunogenicity, and tumor-microenvironment-responsive drug release through genetic engineering [4,137]. For instance, doxorubicin-loaded OMVs derived from attenuated *Klebsiella pneumoniae* (DOX-OMV) efficiently delivered the drug into NSCLC cells, inducing potent cytotoxicity and apoptosis, while also recruiting macrophages to the tumor microenvironment, thereby achieving combined chemo-immunotherapy and significant tumor growth inhibition [138]. Programmable live bacteria have shown preclinical antitumor activity, including *E. coli* Nissle 1917 (EcN) that reprograms metabolism and delivers prebiotics in colorectal cancer [139], and a tumor microenvironment responsive *E. coli* strain that releases CD47 blocking nanobodies to enhance T cell infiltration, induce tumor regression, and inhibit metastasis [140]. However, none of these have been applied to lung cancer or the respiratory microbiota. Future research should engineer strains adapted to the lung niche to enable localized, self-sustaining antitumor therapies that could complement immune checkpoint inhibitors and improve outcomes for lung cancer patients.

Together, aerosolized probiotics, nanomaterial-based antimicrobial platforms, and engineered bacteria offer a range of strategies to directly modulate the lung microbiota, thereby overcoming chemoresistance and enhancing antitumor immunity. While these strategies remain largely at the preclinical stage, their complementary mechanisms—immune regulation, targeted drug delivery, and metabolic reprogramming—hold considerable promise. Future research should focus on translational validation in relevant animal models, optimization of delivery systems for the respiratory tract, and integration with existing immunotherapies. Ultimately, harnessing the lung microbiota through these innovative interventions may open a new frontier in precision oncology for lung cancer.

7. Conclusions and perspectives

This review summarizes the multifaceted roles of the respiratory microbiota in lung cancer. Respiratory microbiota dysbiosis is associated with tumor initiation, metastasis, and poor prognosis. Mechanistically, microbial components promote lung cancer through four main mechanisms: activation of oncogenes and pro-tumoral pathways, epigenetic modulation, metabolic reprogramming and chronic inflammation and immune dysregulation. Beyond bacteria, fungi and viruses also contribute. Specific microbial signatures

show diagnostic, prognostic, and treatment-predictive potential, and early preclinical strategies have demonstrated preclinical efficacy and represent a promising frontier.

Despite these advances, several limitations and knowledge gaps remain (Figure 2). First, Current methods, such as 16S rRNA and metagenomic sequencing, cannot distinguish live/dead microbes and provide only compositional snapshots without functional information. Second, most studies have focused on bacteria, leaving the roles of fungi, viruses, and especially archaea largely unexplored. Third, many findings are merely correlational, and causal relationships between specific microbial species and lung cancer phenotypes remain to be established. Fourth, whether dysbiosis precedes or results from lung cancer (reverse causality) remains unclear, and the temporal direction is unresolved. Fifth, clinical validation of microbiome-based diagnostic and predictive models is lacking, and standardized protocols for sampling, sequencing, and analysis are required. Sixth, interventions directly targeting the pulmonary microbiota remain in early preclinical stages, with no clinical trials having been conducted in lung cancer patients.

To address these gaps, future research should prioritize the following six areas (Figure 2).

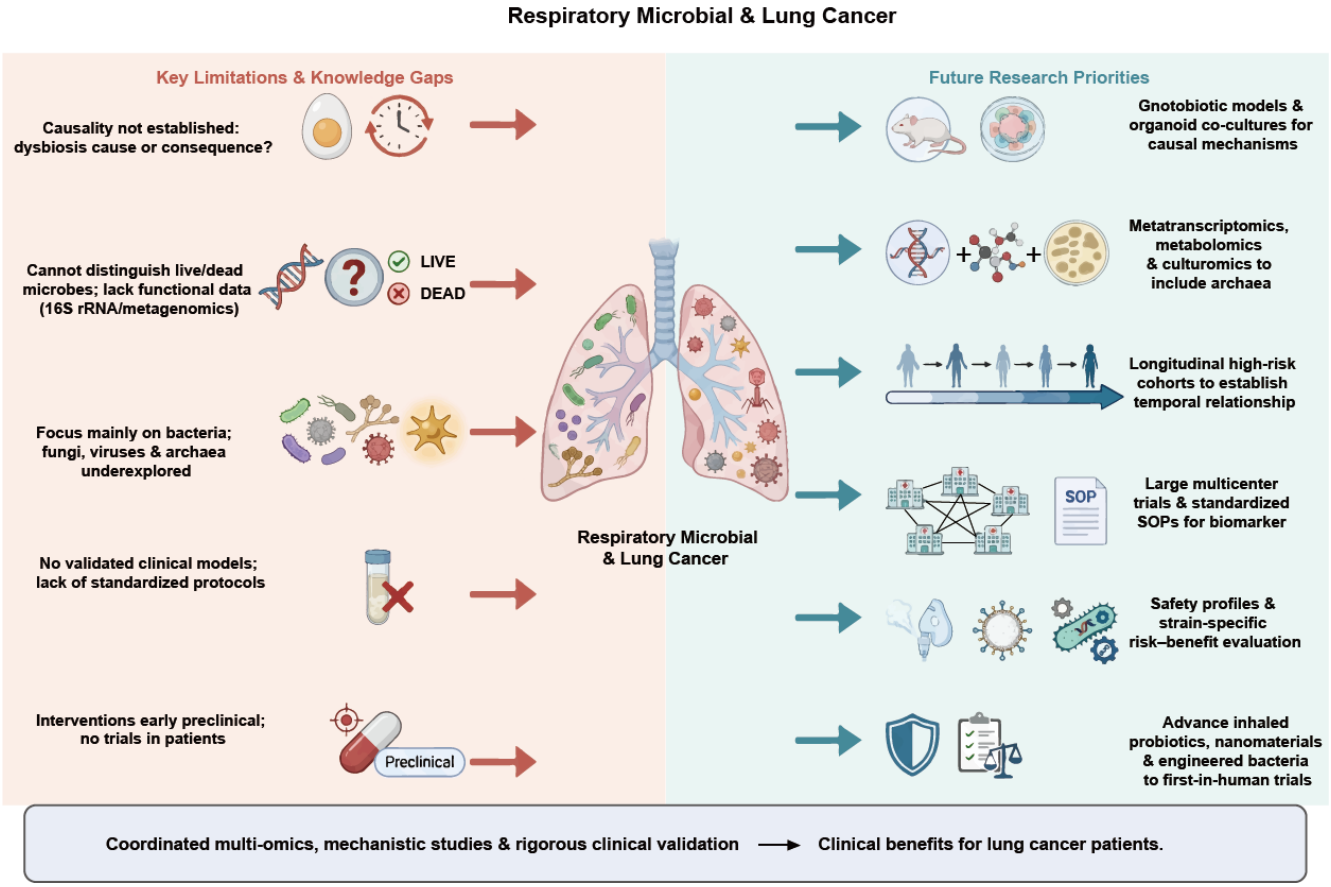

Figure 2. Limitations and future research priorities in respiratory microbiota and lung cancer. (Left) Limitations: ranging from technical issues and underexplored microbial kingdoms to correlative evidence and preclinical-stage therapies; (Right) Future priorities: including multi-omics approaches, causality studies, standardized trials, and clinical development of microbiota-directed interventions. Horizontal arrows connect each limitation to its corresponding priority.

(1) Causality and mechanisms. Use gnotobiotic animal models and organoid-microbe co-cultures to establish causal links and dissect molecular pathways.

(2) Multi-omics integration. Combine metagenomics, metatranscriptomics, metabolomics, and culturomics to obtain functional and mechanistic insights, including the neglected archaeal domain, and broaden profiling to fungi and viruses.

(3) Longitudinal and prospective studies. Follow high-risk cohorts to determine the temporal sequence and causality between dysbiosis and cancer development.

(4) Clinical translation of biomarkers. Validate biomarker panels, including microbial signatures and metabolite/VOC panels in large, multicenter trials with standardized protocols.

(5) Therapeutic interventions require advancing preclinical strategies—such as aerosolized probiotics, microbiota-depleting nanomaterials, and engineered live bacteria—toward first-in-human trials with strain-specific safety evaluation. In addition, delivery systems must be optimized for the unique physiology of the respiratory tract, with considerations including particle size, nebulization, and dry powder inhalers.

(6) Safety and ethics. Assess potential risks of inhaled probiotics and establish strain-specific safety profiles.

In conclusion, the respiratory microbiome plays a significant role in lung cancer biology. Microbial signatures show potential as noninvasive biomarkers for early detection, subtype classification, and prediction of treatment response. Furthermore, direct modulation of the respiratory microbiota represents a novel approach in precision oncology. Although this research area remains at an early stage, coordinated efforts integrating multi-omics, mechanistic studies, and rigorous clinical validation are required to translate these findings into measurable clinical benefits for patients with lung cancer.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. Specifically, the authors used DeepSeek-V4&R1 (locally deployed at Fudan University) for language polishing only in the entire manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the manuscript.

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Authors' Contribution

Conceptualization, Yu Zhao and Shengqing Li; writing—original draft preparation, Yu Zhao; writing—review and editing, Shengqing Li; visualization, Yu Zhao; supervision, Shengqing Li; funding acquisition, Shengqing Li. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Shengqing Li holds the position of Editorial Board Member for *Advanced Cancer Research* and has not peer reviewed or made any editorial decisions for this paper. The authors declare that the research was

conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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