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Review Paper

Lung cancer and the microbiome: Key bacterial players in carcinogenesis and therapy

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ABSTRACT

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non–small cell lung cancer (NSCLC) constituting the majority of cases. Despite therapeutic advances in chemotherapy, targeted therapy, and immune checkpoint inhibitors (ICIs), treatment outcomes remain heterogeneous. Increasing evidence indicates that the human microbiome including the respiratory, gut, and intratumoral compartments plays a crucial role in lung carcinogenesis and therapeutic response. This narrative review synthesizes recent findings on the microbiome's contribution to lung cancer biology and therapy. The healthy lung microbiota is characterized by low biomass yet consistent phyla composition, primarily *Bacteroidetes* and *Firmicutes*, while dysbiosis in lung cancer often features enrichment of *Streptococcus*, *Veillonella*, *Prevotella*, *Haemophilus*, and *Fusobacterium*. These taxa may drive carcinogenesis through immune modulation, chronic inflammation, metabolic signaling, and genotoxic or epigenetic alterations. Beyond the lung, gut microbial diversity and metabolites such as short-chain fatty acids (SCFAs) influence systemic immunity and modulate response to chemotherapy, targeted agents, and ICIs. Antibiotic-induced dysbiosis has been linked to reduced immunotherapy efficacy and shorter progression-free survival in NSCLC cohorts. Emerging microbiome-modulation strategies including probiotics, prebiotics, dietary interventions, fecal microbiota transplantation (FMT), and engineered bacterial therapeutics show promise as adjuncts to precision oncology. However, safety, reproducibility, and mechanistic causality remain major challenges. Collectively, evidence supports the microbiome as a dynamic regulator of lung cancer progression and therapy responsiveness. Future research should prioritize longitudinal, multi-omics investigations and controlled clinical trials to identify predictive microbial biomarkers and develop standardized, personalized microbiome-based interventions for lung cancer management.

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1. Introduction

Lung cancer is a global health challenge, with non-small cell lung cancer (NSCLC) accounting for the majority of cases and carrying a poor 5-year survival rate in advanced stages [1]. Standard treatments, including surgery, chemotherapy, targeted therapy, and immune checkpoint inhibitors (ICIs), have improved outcomes but still suffer from heterogeneous responses and unpredictable resistance [2]. The search for novel biomarkers and modulators of therapy has led to interest in the human microbiome as a potentially influential factor in cancer pathophysiology and therapeutic efficacy. Over the last decade, research has progressively revealed that bacterial communities residing in the respiratory tract, the gut, or even within tumors may interact with host immunity and tumor microenvironment to influence lung carcinogenesis and response to therapy [3-5]. This mini-review aims to focus on key bacterial players reported in the literature over the last decade, map mechanistic hypotheses, and appraise evidence linking bacterial taxa to therapy outcomes in lung cancer.

2. Lung, gut, and intratumoral microbiomes

In the healthy human lung, the resident microbiota is characterized by a relatively low bacterial biomass but a consistent community composition dominated primarily by the phyla *Bacteroidetes* and *Firmicutes*, with additional representation from *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Cyanobacteria* [6]. In healthy lungs, the microbiome composition is shaped by regional physiological factors such as oxygen tension, pH, blood flow, and immune cell activity, as well as by the balance between microbial immigration (mainly via microaspiration) and elimination through mucociliary clearance and immune defenses. These dynamic interactions maintain a stable yet adaptable microbial ecosystem within the lung. However, sampling lungs is technically challenging and prone to contamination, making robust interpretation difficult [6]. Comparative studies suggest that lung microbiome composition is altered in disease states and in cancer [3]. The gut-lung axis refers to bidirectional communication between gut microbiota and respiratory tract immunity or homeostasis [5]. Gut bacteria produce metabolites (e.g. short-chain fatty acids, [SCFAs]) or microbial-associated molecular patterns (MAMPs) that may enter systemic circulation or modulate systemic immune tone, thereby affecting lung tissue [5, 7]. In recent years, evidence has emerged that tumors themselves may harbor intratumoral bacteria, which can interact locally with cancer and stromal cells, influence metabolic pathways, and modulate immune cell infiltration [8, 9].

3. Key bacterial taxa linked to lung cancer: Evidence Summary

Multiple studies over the past decade have identified bacterial taxa whose relative abundance differs between lung cancer patients and controls, or among subgroups of patients (e.g. responders vs. nonresponders). *Streptococcus* often enriched in lung tumor or airway samples; implicated in upregulation of ERK/PI3K signaling in airway epithelia. *Veillonella* reported in several studies of lower airway microbiota, sometimes co-enriched with *Streptococcus* in lung cancer settings [10-12].

Several studies have implicated *Prevotella* enrichment in lung tissues as a potential marker of poor prognosis and recurrence in lung adenocarcinoma. In lung cancer patients, *Prevotella*, along with other oral commensals such as *Veillonella* and *Streptococcus*, has been associated with tumor progression and activation of pro-cancer signaling pathways such as IL-6/IL-8, PI3K/ERK, and p53 pathways. Thus, *Prevotella* may influence the lung tumor microenvironment by modulating inflammatory signaling and host-microbe interactions that favor cancer development [13-15].

Haemophilus observed in some lung cancer-associated airway microbial profiles, sometimes linked to Proteobacteria expansion.

Recent analyses show that Haemophilus, notably non-typeable Haemophilus influenzae (NTHi), is enriched in lung cancer tissues compared to healthy lung, suggesting a possible association with tumor environments.

NTHi is known to induce strong and persistent inflammatory responses in the lung by activating innate immune pathways, which may contribute to chronic inflammation and thereby potentially promote carcinogenesis, especially in the context of smoking and chronic lung injury [3,16].

Fusobacterium/*Porphyromonas* frequently discussed in the context of oral-lung microbial translocation; some studies implicate them in carcinogenesis via proinflammatory or genotoxic mechanisms. Emerging evidence links *Fusobacterium*, especially *F. nucleatum*, to poorer outcomes in lung cancer; airway enrichment of *Fusobacterium* is associated with reduced response to anti-PD-1 therapy.

F. nucleatum may also act as an “oncobacterium,” influencing tumor mutation burden and promoting a more aggressive tumor phenotype. In parallel, *Porphyromonas* species, particularly *P. gingivalis* show higher colonization rates in lung carcinoma tissues, correlate with advanced clinical stage and lymph node metastasis, and are linked to worse survival. Their potential mechanistic roles include modulating the tumor microenvironment or even directly promoting malignant progression via inflammatory signaling [3,16-18].

Many studies find elevated relative abundance of Proteobacteria in lung cancer samples compared to controls [3,18]. While many human studies are cross-sectional, some cohort-level analyses correlate bacterial abundance or diversity with tumor stage, metastasis, or survival [3,4].

4. How bacteria may promote or inhibit carcinogenesis?

Several mechanistic hypotheses have been proposed to connect bacterial presence or dysbiosis to lung cancer initiation or progression. Immune modulation and chronic inflammation: Bacteria may stimulate innate receptors (e.g. TLRs, NLRs) on epithelial or immune cells, provoking cytokine release (IL-6, TNF-α, IL-17), recruitment of myeloid cells, and a proinflammatory microenvironment conducive to tumor initiation [7,19]. Metabolite/molecular mediators: Bacterial metabolites (e.g. SCFAs, secondary bile acids, microbial toxins) or lipopolysaccharide (LPS) may reach lung tissue via circulation, influencing epithelial cell proliferation, apoptosis resistance, or DNA damage [20,21]. Intratumoral interaction: Bacteria within tumors may affect local nutrient availability, produce reactive oxygen species (ROS), modulate tumor cell signaling pathways (e.g. ERK, PI3K), or impact immune cell infiltration or exhaustion [9,22]. Epigenetic or genotoxic effects: Some bacterial products may act as genotoxins that damage DNA or influence epigenetic regulation, promoting mutational burden or dysplasia over time. These combined genotoxic and epigenetic alterations contribute to disruption of normal gene regulation, silencing of tumor suppressors, activation of oncogenes, and promotion of a tumor-friendly microenvironment [23,24]. It is also plausible that certain bacteria may exert protective effects (via immunostimulation or competition), although direct evidence in lung cancer is limited.

5. Bacterial influence on therapy: Chemotherapy, targeted therapy, and immunotherapy

Recent studies increasingly show that the composition and function of the host microbiota, particularly gut bacteria play a key modulatory role in the efficacy, toxicity, and resistance profiles of cancer therapies, including chemotherapy, targeted therapy, and immunotherapy [25,26]. In chemotherapy, gut bacteria can directly metabolize drugs, alter their pharmacokinetics, or produce enzymes that degrade or activate chemotherapeutic agents; moreover, severe dysbiosis, often induced by antibiotics, may exacerbate side effects (such as mucositis) or reduce drug efficacy via altered immune modulation [27]. In targeted therapies, recent work highlights that intestinal bacteria and their metabolites can interfere with signalling pathways relevant to drug targets (e.g. EGFR, VEGF, HER2), either by modulating systemic inflammation or by affecting drug absorption and resistance, thus influencing outcomes of precision medicine approaches [28].

Further, immunotherapy efficacy (notably with ICIs) is strongly associated with the diversity and specific taxa of gut microbes; studies have found that prior or concurrent antibiotic exposure can diminish responses, reduce progression-free and overall survival, and that certain bacterial genera (e.g. members of Ruminococcaceae, Firmicutes, or Akkermansia) are overrepresented in responders [27,29]. In the lung cancer context, observational studies in NSCLC patients suggest that higher gut microbial diversity at baseline correlates with longer progression-free survival and better response to ICIs [26]. Use of antibiotics prior to or during immunotherapy is often associated with poorer ICI outcomes in lung cancer cohorts [26].

These observations suggest that therapeutic modulation of the microbiota (via probiotics, fecal microbiota transplantation, or precision microbiome engineering) offers a promising adjunct to conventional, targeted, and immune-based cancer treatments, though substantial challenges remain such as reproducibility across patients, safety, and identifying consistent microbial biomarkers.

6. Microbiome-modulation strategies

A key modality to enhance cancer therapy efficacy is through deliberate modulation of the gut microbiome; Ren et al. demonstrated in NSCLC that higher baseline microbial diversity and elevated levels of SCFAs correlate with better responses to immunotherapy, and that fecal microbiota transfer (FMT) from responding patients to murine models improved tumor control and potentiated immunotherapy effects [30]. Such results support the concept that microbiome interventions via probiotics, prebiotics, engineered bacterial strains, dietary fiber, or FMT can shift microbial community structure in favor of taxa that promote antitumor immunity (e.g. through enhanced SCFA production, immune cell priming, or modulation of checkpoint pathways) [31]. Moreover, predictive models trained on microbial taxonomic and functional features have shown promising accuracy in forecasting immunotherapy responses, thereby offering a rational basis for personalized microbiome strategies that complement conventional and immune-based cancer treatment [32]. These mechanisms and microbiome-targeted interventions are summarized in Figure 1. However, challenges persist in standardizing donor selection, engraftment stability, and safety considerations, especially in immunocompromised patients.

7. Future directions and research recommendations

Future work should focus on translating microbiome-oncology associations into reproducible clinical tools and therapeutic strategies. Longitudinal multi-center cohorts are required to monitor microbiome shifts across disease stages and treatment cycles, enabling the identification of dynamic microbial signatures predictive of therapy response or toxicity [5].

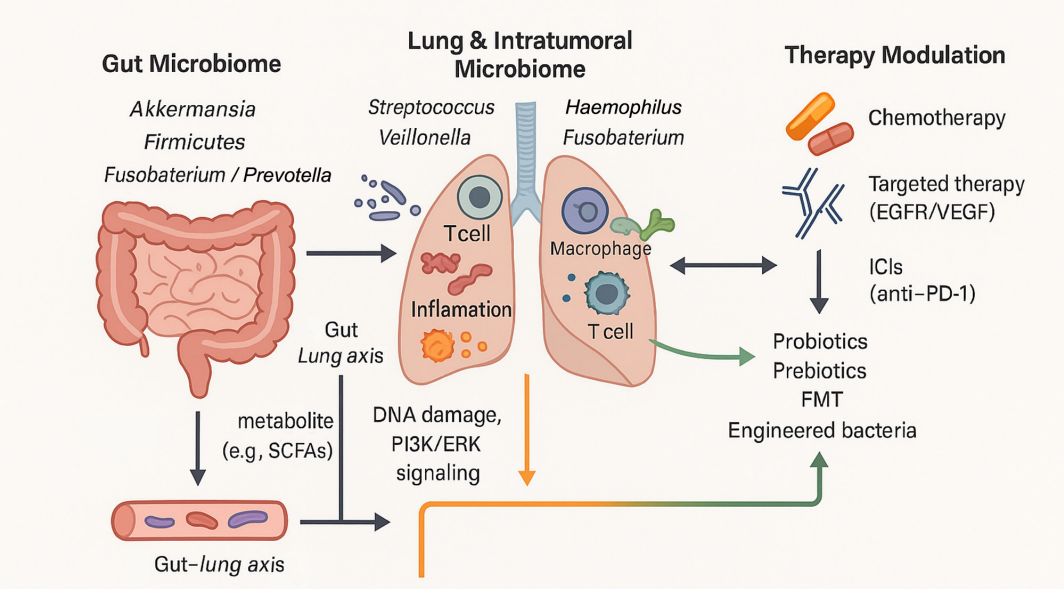

Figure 1. Schematic overview illustrating the interplay between the gut, lung, and intratumoral microbiomes in lung cancer. Bacteria influence carcinogenesis and therapy outcomes through immune modulation, metabolite signaling, and genotoxic pathways, while microbiome-targeted interventions (probiotics, FMT, engineered bacteria) offer emerging therapeutic potential.

Integration of multi-omics including metagenomics, metabolomics, host transcriptomics, and spatial profiling will clarify causal links between bacterial function and tumor-immune interactions [33,34]. Randomized clinical trials should assess microbiome-modulation interventions such as probiotics, prebiotics, or FMT in combination with ICIs or chemotherapy, while maintaining rigorous safety monitoring [31]. Furthermore, standardization of sample collection, sequencing depth, and contamination control, particularly in low-biomass lung specimens is critical for reproducibility [3]. Bioinformatic pipelines that harmonize microbial and host data will facilitate discovery of bacterial biomarkers and mechanistic pathways relevant to personalized lung cancer therapy. Finally, future research should explore engineered bacterial vectors capable of targeted intratumoral delivery of immunomodulatory or cytotoxic molecules, a promising frontier that merges synthetic biology with oncology [29].

8. Conclusion

Mounting evidence highlights that the lung, gut, and intratumoral microbiomes actively modulate lung cancer pathogenesis and therapeutic outcomes. Specific bacterial taxa emerge as recurrently associated with tumor progression, inflammation, or immune evasion. Mechanistic data suggest these microbes influence carcinogenesis through immune activation, genotoxicity, and metabolic signaling. Parallel findings reveal that gut microbial diversity and metabolite profiles shape the efficacy of chemotherapy, targeted agents, and especially ICIs. Consequently, microbiome-modulation strategies including dietary interventions, probiotics, FMT, and engineered bacterial therapeutics represent promising adjuncts to precision oncology. Nevertheless, major challenges remain in establishing causal relationships, ensuring patient safety, and achieving reproducible microbial signatures across diverse populations. Progress in this rapidly evolving field will depend on harmonized clinical protocols, functional validation of candidate microbes, and translational studies that bridge laboratory discovery to bedside application.

Authors' contributions

NK: Methodology, investigation, and NK: writing original draft. MF: Conceptualization, writing review, and critically revised the manuscript for important intellectual content. Both authors have read and approved the final version of the manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

Not applicable.

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