Trends in
Molecular Medicine

CellPress

Review

Harnessing the lung microbiome for precision management of fibrotic lung disease

Sylvie Leroy[1,2], Barnabé Roméo[1], Amine Belaid[1], Patrick Brest[1], Charles-Hugo Marquette[1,2], Valérie Vouret-Craviari[1], Véronique Hofman[1,3], Paul Hofman[1,3,#], and Baharia Mograbi[1,*,#]

Interstitial lung diseases, particularly idiopathic pulmonary fibrosis (IPF), have dismal prognoses, with a median survival of 3–5 years, owing to a lack of early biomarkers or effective treatments. This review highlights the lung microbiome as a key biological factor in IPF pathogenesis and a promising therapeutic target. Elevated burdens of pathogenic bacteria, including *Streptococcus* and *Staphylococcus*, in bronchoalveolar lavage fluid correlate with accelerated progression and higher mortality. These bacteria release toxins and activate Th17-driven inflammation, providing mechanistic links to alveolar injury and fibrosis. Host genetics and systemic factors, including oral–gut–lung interactions, further shape disease progression. Although antibiotic trials have been unsuccessful, embracing the microbiome as an active participant in IPF may open unprecedented opportunities for personalized interventions.

Highlights

The lungs contain a dynamic microbial ecosystem that influences respiratory immunity, inflammation, and fibrosis in interstitial lung disease (ILD).

An elevated bacterial burden in bronchoalveolar lavage fluid emerges as an independent predictor of idiopathic pulmonary fibrosis.

Dysbiosis featuring *Streptococcus*, *Staphylococcus*, and *Haemophilus* accelerates disease progression by promoting epithelial injury and sustained Th17-mediated profibrotic responses.

Bidirectional oral–lung and gut–lung microbial axes modulate pulmonary fibrosis via microaspiration events and circulating metabolites, including short-chain fatty acids and tryptophan derivatives.

Microbiome profiling and therapeutics that selectively eliminate pathogenic taxa while preserving beneficial commensals hold promise for early diagnosis and personalized treatment in ILD.

Breaking the silence: how the lung microbiome reshapes respiratory biology

For over a century, the healthy lung was regarded as a sterile sanctuary, protected by immune defenses and mucociliary clearance—a dogma that profoundly shaped respiratory medicine by treating any microbe as a pathogen to be eradicated. However, recent sequencing technologies have revolutionized this view, revealing the lung as a dynamic ecosystem colonized by bacteria, fungi, and viruses that actively shape respiratory health and disease. Among conditions now recognized as microbiome-influenced are interstitial lung diseases (ILD), a diverse group of pulmonary disorders characterized by inflammation and fibrosis, with a European incidence of 20–42.5 cases per 100 000 person-years [1]. Idiopathic pulmonary fibrosis (IPF), the most severe ILD subtype, carries a median survival of 3–5 years, similar to many aggressive cancers, making understanding of disease mechanisms critically important [2].

This review synthesizes current evidence, positioning the lung microbiome as a crucial driver rather than a bystander in ILD pathogenesis, with significant translational implications. Key advances include the identification of **bacterial burden** (see Glossary) as an independent predictor of mortality, specific pathogenic taxa that accelerate fibrotic progression, and the emerging importance of the **oral–lung axis** and **gut–lung axis** in disease development. **Microbial dysbiosis** initiates a vicious cycle in which epithelial injury leads to immune dysfunction and fibrotic remodeling, creating new niches for pathogenic colonization that sustain disease progression. These insights enable the development of microbiome-based biomarkers for early diagnosis and novel therapeutic strategies to restore microbial–immune homeostasis, potentially interrupting the fibrotic cascade at its source rather than merely managing symptoms (Figure 1).

The microbial universe within: understanding lung ecology

The lung microbiome is a dynamic, low-biomass ecosystem characterized by the ‘adapted island model’, where microbial composition and abundance are shaped by immigration, replication, and

[1]Université Côte d’Azur, Institute for Research on Ageing and Cancer, Nice (IRCAN), Institut Hospitalo-Universitaire (IHU) RespirERA, Fédérations Hospitalo-Universitaires (FHU) OncoAge, Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM), Nice 06107, France
[2]Department of Pulmonary Medicine and Thoracic Oncology, Centre Hospitalier Universitaire (CHU) de Nice, FHU OncoAge, IHU RespirERA, Nice 06000, France
[3]Laboratory of Clinical and Experimental Pathology (LPCE), Biobank (BB-0033-00025), Centre Hospitalier Universitaire (CHU) de Nice, FHU OncoAge, IHU RespirERA, Nice 06000, France
[#]These authors contributed equally.

© 2026 Elsevier Ltd. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

*Correspondence:
baharia.mograbi@univ-cotedazur.fr
(B. Mograbi).

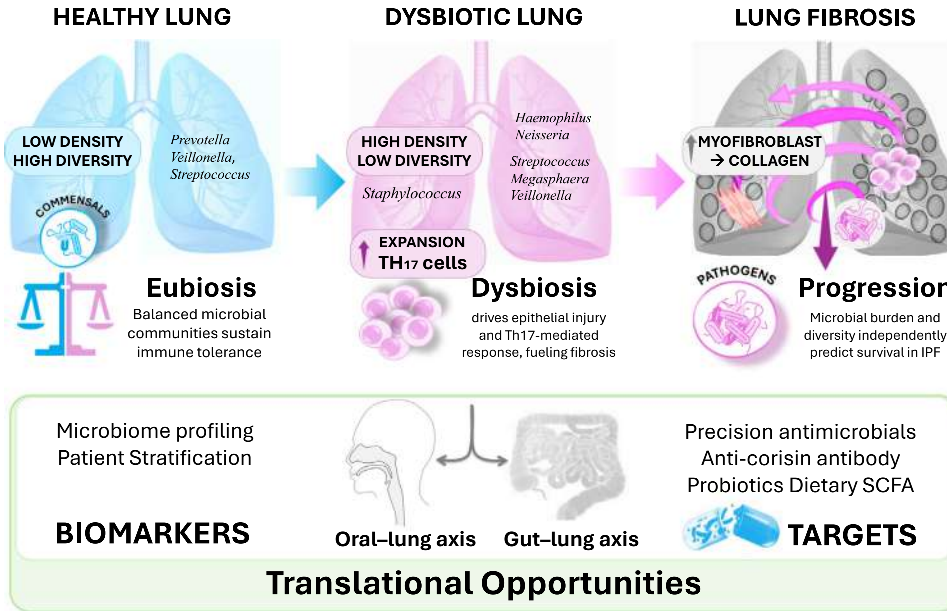

Figure 1. Lung microbiome dysbiosis as a driver of immune activation and fibrotic remodeling in idiopathic pulmonary fibrosis. In healthy lungs, the microbiome is characterized by low bacterial density and high microbial diversity, dominated by commensal taxa that contribute to immune homeostasis. In idiopathic pulmonary fibrosis (IPF), this balance is disrupted, leading to increased bacterial burden and reduced diversity, accompanied by the expansion of specific genera, including *Staphylococcus*, *Haemophilus*, *Neisseria*, and *Streptococcus*. This dysbiotic state is associated with heightened mucosal immune activation, notably the expansion of TH17 cells, which promotes profibrotic signaling. Sustained immune–microbial interactions contribute to fibroblast activation, myofibroblast accumulation, and excessive collagen deposition, driving progressive lung fibrosis. At the translational level, microbiome profiling enables patient stratification and biomarker discovery. Therapeutic opportunities include precision antimicrobials, neutralization of microbial virulence factors (e.g., anticorisin antibodies), and microbiome-modulating strategies targeting the oral–lung and gut–lung axes, including probiotics and dietary short-chain fatty acid (SCFA) interventions.

elimination processes [3]. Immigration is the primary pathway for microorganisms entering the lung environment, primarily through **microaspiration** of oropharyngeal contents. This physiological process continuously introduces microbes from the mouth and throat into the lower respiratory tract during sleep. Other routes include inhalation of environmental microbes and, occasionally, hematogenous seeding from distant infection sites. Replication occurs once microorganisms establish themselves in lung niches. They must adapt to environmental challenges, including variable oxygen levels, limited nutrients, exposure to antimicrobial peptides, and immune surveillance. Microbial species that possess metabolic flexibility and resistance to host defenses can thrive, with some, especially those capable of forming biofilms, persisting despite clearance mechanisms. Elimination is the lung's innate defense against microbial overgrowth. This includes mucociliary transport, which moves particles and microbes toward the throat, alveolar macrophage phagocytosis, which destroys potential pathogens, and the production of antimicrobial peptides and surfactant proteins, which directly inhibit microbial growth. When these mechanisms are compromised, microbial communities can expand and shift toward more harmful compositions, leading to disease [4].

CellPress

Defining the lung microbiome: from sterile to symbiotic lungs

The emergence of sequencing platforms and **metagenomics** (Boxes 1 and 2) has revolutionized the characterization of the lung microbiome [6,7]. Microbiomes previously unattainable by conventional culture techniques were identified through PCR amplification and **16S rRNA gene sequencing** [8]. When applied to respiratory samples, such as **bronchoalveolar lavage (BAL)** fluid from IPF patients, this cost-effective method enables profiling of bacterial communities at the genus and species levels, unlocking new insights into respiratory health. However, it is essential to acknowledge that sequencing the conserved 16S rRNA gene cannot differentiate between closely related bacterial strains. **Shotgun metagenomic sequencing** simultaneously captures host DNA and the genomes of bacteria, viruses, and fungi, offering comprehensive identification of the entire microbial microbiome. Additionally, newly developed **metatranscriptomic** methods that sequence all RNA transcripts have already linked specific microbial activities to poor outcomes in lung disease [9–11].

Although still in the early stages of characterization, the lung microbiome is now recognized as a unique community of metabolically active organisms that produce immunomodulatory metabolites [9,10]. The lung microbiome is defined by several key features that collectively shape respiratory health and disease. ‘Microbial diversity’ (α-diversity) measures the richness and evenness of a microbial community, reflecting the stability and resilience of the ecosystem within a sample. A reduction in diversity is often associated with dysbiosis and adverse clinical outcomes. ‘Community composition’ (β-diversity) refers to the taxonomic structure of microbial communities, which varies significantly between healthy individuals and those with disease. Changes in community composition can often precede the clinical manifestations of disease progression. ‘Bacterial burden’ (biomass) refers to the absolute quantity of microbial material present and serves as a crucial biomarker for determining disease severity and prognosis across various ILD subtypes.

Box 1. Complementary sequencing approaches for lung microbiome profiling: 16S rRNA versus shotgun metagenomics

Two principal sequencing strategies dominate lung microbiome research, each with advantages and limitations that influence their suitability for different research questions and clinical applications (Figure I).

‘16S rRNA gene sequencing’ is the most used method for profiling bacterial communities. This technique targets the highly conserved 16S ribosomal RNA gene, which contains hypervariable regions that enable reliable bacterial identification. The process involves extracting DNA, amplifying the 16S gene using universal primers through PCR, and sequencing the resulting amplicons. This method provides several benefits: a low cost ($50–100 per sample), compatibility with low-biomass microbiome typical of lung samples, and the ability to enrich bacterial DNA relative to abundant host DNA. Moreover, well-established bioinformatic pipelines and comprehensive reference databases make analysis straightforward.

However, 16S sequencing has notable limitations: its resolution typically reaches the genus level and cannot differentiate between closely related species or strains. Additionally, 16S sequencing provides no functional information on antimicrobial resistance genes, virulence factors, or metabolic capabilities. PCR amplification introduces bias through primer mismatches, and the method does not detect fungi or viruses. The results are solely expressed as relative abundance percentages, without indicating the actual bacterial load.

‘Shotgun metagenomic sequencing’ overcomes many of these limitations by sequencing all DNA in a sample without PCR amplification. This PCR-free workflow enables species and strain-level resolution, detection of functional genes, and simultaneous profiling of bacteria, fungi, and viruses. Nevertheless, these benefits come with high costs: $500–1000 per sample (5–10 times more expensive than 16S), complex bioinformatics requiring specialized expertise and computational resources, and increased sensitivity to contamination, as over 90% of sequences typically derive from human host DNA even with deep sequencing. The large volume of data demands advanced quality control and decontamination strategies.

The complementary nature of these approaches supports population-level comparisons of microbiomes. A hybrid analytical approach that combines initial screening of large patient cohorts with cost-effective 16S sequencing identifies taxonomic patterns and formulates hypotheses. Shotgun metagenomics is then selectively applied to samples of mechanistic interest that require species-level identification or functional characterization.

Glossary

16S rRNA gene sequencing: a molecular method that identifies bacteria by amplifying and sequencing the universal bacterial gene (16S rRNA). It reveals which bacterial genera are present but cannot distinguish closely related species or provide information about microbial metabolic activities.

Bacterial burden: the total amount of bacteria in a sample, measured using quantitative PCR targeting the 16S rRNA genes and expressed as copies per milliliter. In IPF, a bacterial burden exceeding 10^6 copies/ml in BAL fluid predicts worse survival.

Bronchoalveolar lavage (BAL): a clinical procedure where sterile saline is instilled into the lung and immediately aspirated through a bronchoscope. The retrieved fluid contains cells, proteins, and microbes from the lower respiratory tract for diagnostic purposes.

Dysbiosis: a disruption in microbial communities characterized by increased bacterial load, a loss of beneficial commensals, overgrowth of pathogenic organisms, and decreased diversity.

Gut–lung axis: bidirectional communication between the intestinal and respiratory systems via microbial metabolites, immune cells, and inflammatory mediators. Gut dysbiosis can worsen lung inflammation by reducing anti-inflammatory (SCFAs) and promoting proinflammatory (kynurenine) metabolites.

Interleukin-17B (IL-17B): a cytokine that promotes collagen deposition, fibroblast activation, and neutrophil inflammation. Bacterial components, such as outer membrane vesicles, stimulate IL-17B production, aggravating IPF progression.

Metagenomics (shotgun): a comprehensive sequencing method that captures all DNA in a sample without targeted amplification. It identifies bacteria, fungi, viruses, and functional genes for virulence, antimicrobial resistance, and metabolism. However, it is more costly and data-intensive than 16S sequencing.

Metatranscriptomics: the sequencing of all RNA transcripts in a microbial community sample, providing a snapshot of which genes are actively expressed. It distinguishes active microbes from dormant ones and uncovers metabolic or inflammatory pathways operating in diseased lungs.

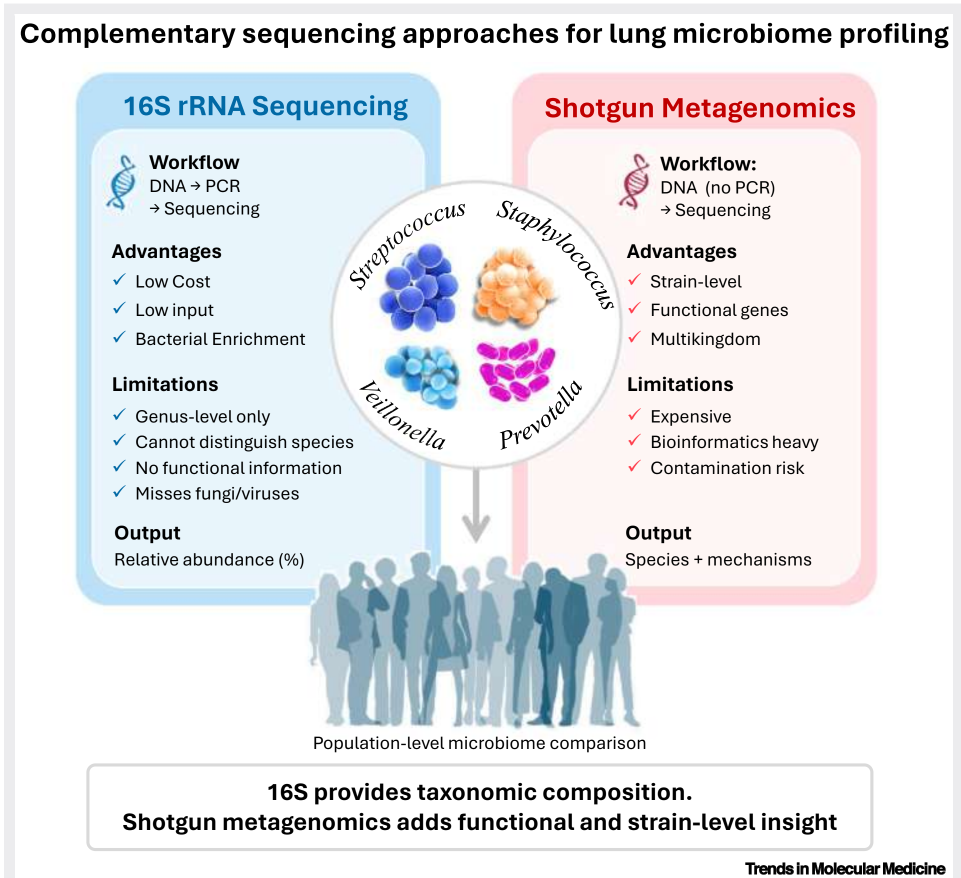

Figure I. Complementary sequencing approaches for lung microbiome profiling. Comparison of 16S rRNA gene sequencing (left, blue panel) and shotgun metagenomics (right, pink panel) for bacterial community analysis. The central illustration depicts representative lung bacteria (*Streptococcus*, *Staphylococcus*, *Veillonella*, and *Prevotella*) analyzed by both methods.

Microaspiration: subclinical entry of oropharyngeal contents into the lungs. While physiologically occurring during sleep, it becomes excessive with esophageal dysmotility or reflux, leading to the introduction of oral bacteria into the lungs and provoking inflammation.
Oral–lung axis: the microbial connection between the oral cavity and lungs, mainly via repeated microaspiration. Oral commensals such as *S. mitis* are harmless in the mouth but can trigger inflammation when they colonize the lungs, activating Toll-like receptors and Th17 responses.
Shannon diversity index: a mathematical measure combining the number and distribution of microbial species. BAL fluid values below 2.5 indicate dysbiosis and are associated with faster IPF progression and a higher risk of mortality.
Short-chain fatty acids (SCFAs): small molecules (acetate, propionate, and butyrate) produced by gut microbes from dietary fiber. SCFAs have anti-inflammatory properties and help regulate immunity; their depletion during gut dysbiosis can intensify lung inflammation.
Th17 cells: a subset of CD4$^+$ T helper lymphocytes that produce IL-17 and proinflammatory cytokines. While essential for defending mucosal surfaces against microbes, their persistent stimulation by microbial products sustains lung inflammation and fibrosis.

The IPF connection: when microbe burden predicts mortality

The relationship between the lung microbiome and IPF outcomes is one of the most significant discoveries in respiratory medicine. High-throughput 16S rRNA sequencing has revealed that IPF patients exhibit higher bacterial burdens in BAL fluid than healthy individuals and those with chronic obstructive pulmonary disease [8]. More remarkably, this increased bacterial load has emerged as a predictor of mortality, a prognostic value confirmed across multiple cohorts [12–14]. Patients with rapid functional decline consistently exhibit higher baseline bacterial loads, which rise significantly during acute exacerbations [11,15].

This observation raises a provocative 'chicken-and-egg' question: does microbial colonization actively drive disease progression, or does it emerge as a secondary consequence of the fibrotic remodeling that creates favorable niches for bacterial growth [16,17]? Although the causal link in human IPF remains unestablished, several lines of evidence favor a contributory role for dysbiosis. Notably, bacterial burden is independently associated with mortality, even after adjustment for established structural markers of disease severity, including forced vital capacity, honeycombing, traction bronchiectasis, and architectural distortion [13]. Moreover, honeycombing, the radiographic hallmark of end-stage fibrosis, shows no correlation with bacterial load [18,19]. This

dissociation argues against the hypothesis that increased bacterial burden merely reflects an epiphenomenon of advanced disease. Instead, it suggests that microbial expansion may actively participate in fibrotic progression.

The strongest mechanistic support comes from germ-free mouse models, in which the absence of microbes reduces lung fibrosis and improves survival compared with colonized counterparts [12,20,21]. These mouse models provide proof of biological feasibility but should not be interpreted as direct evidence of causality in human IPF, given species-specific immune–microbial interactions and experimental injury paradigms. In line with this, the protective effect in the lung contrasts sharply with the gut, where germ-free mice still develop aberrant intestinal immune responses [22–25], cautioning against extrapolating intestinal paradigms to the lung. These findings reinforce the notion that the lung and gut ecosystems, though interconnected, operate under fundamentally different microbial–immune principles.

A puzzling spatial paradox: distant microbes and local fibrosis

Yet these observations have opened a Pandora's box of mechanistic questions. A major challenge to direct causal interpretation lies in the spatial paradox of the IPF microbiome. Multiple explant-based studies demonstrate that bacterial communities predominantly localize to bronchiolar niches distal to primary fibrotic foci, which are relatively sterile [26,27]. How do these microbes, spatially separated from fibrotic tissue, exert such significant effects on disease progression? Rather than undermining microbial involvement, this spatial disconnect reframes it

Box 2. Technical challenges and quality control strategies in low-biomass lung microbiome analysis

Identifying the lung microbiome remains a significant challenge, owing to its low bacterial biomass. With only about 10^3–10^5 bacteria per milliliter of BAL fluid, approximately 1000-fold fewer than in the gut, this scarcity makes lung samples particularly prone to contamination during processing and analysis [5].

Contamination can emerge from three primary sources (Figure I): (i) Oral microbiota carryover: During bronchoscopy, instruments traverse the oropharynx, introducing oral commensals such as *Streptococcus*, *Prevotella*, and *Veillonella* into lung samples. (ii) Reagent contamination (called 'kitomes'): DNA extraction kits and PCR reagents can harbor trace amounts of bacterial DNA introduced during manufacturing. Notable contaminants include *Ralstonia*, *Cupriavidus*, and *Burkholderia*. (iii) Environmental contamination and sequencing artifacts: airborne particles, surfaces, and personnel can introduce bacteria such as *Acinetobacter*, *Sphingomonas*, and *Staphylococcus*.

Essential negative controls

To distinguish lung microbiota from contaminants, it is essential to include five negative controls in every study: (i) Patient oral rinsing with sterile saline before bronchoscopy to minimize oral bacterial load. (ii) Bronchoscope rinses with sterile saline to assess equipment-related contamination. (iii) Extraction blanks prepared with sterile water and processed identically to biological samples to detect reagent-derived contamination. (iv) PCR-negative controls that amplify without template DNA to identify contamination in PCR reagents. (v) Laboratory air controls collected by passive sampling using open sterile plates in the bronchoscopy suite and laboratory to capture airborne bacteria that may compromise profiling.

All negative controls should be sequenced to the same depth as the samples. Tools such as the decontam R package help identify and remove contaminants by comparing contaminant prevalence across samples and controls. Taxa appearing at similar frequencies are flagged as likely contaminants and excluded.

Anatomical limitations and challenges for clinical translation

Beyond contamination, BAL-based microbiome profiling also faces anatomical constraints. BAL fluid typically samples the bronchial and bronchiolar compartments and may not accurately reflect microbial involvement in the fibrotic parenchyma, which is relatively sterile compared with the airways. This spatial disconnect raises questions about associations between the microbiome and outcomes.

Furthermore, the proposed prognostic threshold of 10^6 16S rRNA gene copies/ml faces significant barriers to routine clinical use. Interlaboratory variability in qPCR protocols and a lack of standardization in BAL collection and processing contribute to considerable pre-analytical heterogeneity. Until multicenter studies establish harmonized protocols and validate threshold reproducibility, bacterial burden quantification remains a research tool rather than a validated clinical biomarker.

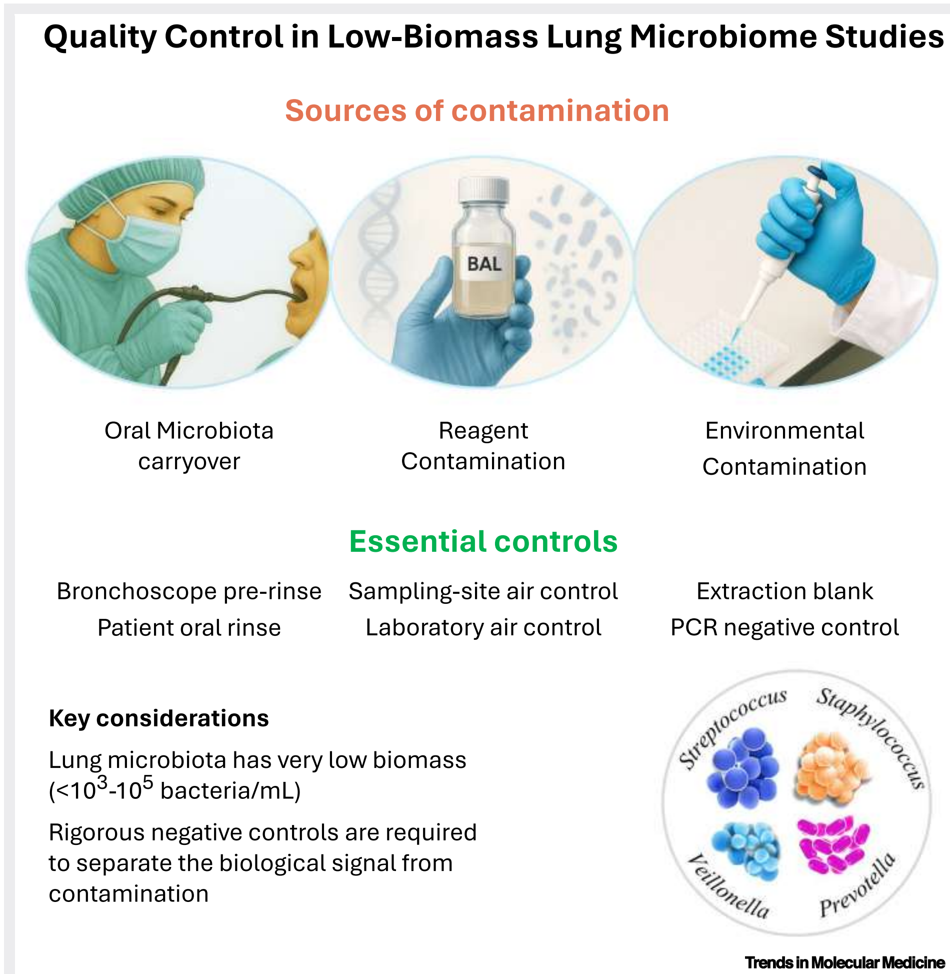

Figure I. Sources of contamination and essential quality controls in low-biomass lung microbiome studies. Sources of contamination in lung microbiome studies span the sampling procedure, the BAL fluid itself, and downstream laboratory handling. Implementing rigorous technical controls is essential to distinguish low-biomass signals from artifacts. BAL: bronchoalveolar lavage.

as a more complex, indirect mechanism through immune activation. Microbes likely orchestrate fibrotic progression through soluble mediators, immune cell trafficking, or paracrine signaling that bridge the bronchiolar and parenchymal compartments. We propose that dissecting the implications of this spatial paradox may hold the key to understanding IPF pathogenesis and, ultimately, to therapeutic intervention.

Beyond numbers: the taxonomic fingerprint of disease

In patients with IPF, beyond the biomass, the lung microbiome's composition is also altered. Notably, the abundance of harmful bacterial genera in BAF fluid has been linked to faster disease progression and a higher mortality risk. Key IPF taxa include *Streptococcus, Prevotella*, and *Veillonella*, suggesting a shift toward oral-associated anaerobes. However, the pathogenic potential of these genera, particularly *Streptococcus*, is context-dependent and cannot be inferred solely from taxonomic identification, underscoring the need to characterize these microbes *in situ*.

Staphylococcus emerges as a significant player in IPF pathogenesis, demonstrating remarkable adaptation to the high-salt microenvironment of the fibrotic lung [28,29], where TGF-β-mediated disruption of sodium transport [30] creates favorable conditions for halophilic species. *Staphylococcus* produces corisin, a proapoptotic peptide that becomes elevated in the BAL fluid of IPF patients and reaches even higher concentrations during acute exacerbations [28]. The therapeutic potential of targeting corisin has been demonstrated in preclinical models, where monoclonal antibody-mediated neutralization successfully ameliorated experimental lung fibrosis [31].

Streptococcus species present a more nuanced picture. An increased abundance of *Streptococcus* units in BAL fluid was identified as a predictor of disease progression and an increased mortality risk in the landmark COMET study [32]. Mechanistically, *Streptococcus pneumoniae* contributes to lung injury by producing pneumolysin, a toxin that induces alveolar epithelial cell death in preclinical models [33]. Together, pneumolysin from *S. pneumoniae* and corisin from *Staphylococcus* species directly cause epithelial cell death, fueling the cycle of injury and abnormal repair characteristic of IPF. Moreover, ongoing exposure to *Streptococcus* products maintains profibrotic Th17 inflammatory responses, which prevent the resolution of tissue repair and promote progressive scarring [34,35]. Yet, as discussed in the section 'The oral–lung axis: gateway to disease', not all *Streptococcus* species exert equivalent effects. This duality highlights the limitations of genus-level taxonomic analysis and emphasizes the urgent need for species- and strain-resolved functional studies.

The consistent identification of these taxa across multiple longitudinal studies suggests that microbial signatures hold promise for improving how we stratify risk and target therapies in IPF populations. While bacterial burden and composition remain relatively stable within individuals, they diverge dramatically across disease trajectories, suggesting that microbial communities could serve as prognostic biomarkers. However, clinical translation will require standardized sampling, validated thresholds, and, crucially, a deeper understanding of microbial function beyond taxonomic presence.

The diversity paradox: when less means worse clinical outcomes

Reduced lung microbial diversity is emerging as a key feature of IPF-related dysbiosis, highlighting the complex interaction between microbes and disease. In patients with IPF, lower **Shannon diversity indices** in BAL fluid are associated with adverse outcomes, including increased bacterial burdens, elevated proinflammatory cytokines, a faster decline in lung function, and decreased survival rates [12,36]. This diversity paradox, in which low microbial diversity correlates with worse outcomes, mirrors the gut microbiome patterns where decreased richness signals ecosystem instability [37,38], suggesting that balanced communities prevent pathogenic overgrowth through niche competition. The expansion of pathogenic bacteria, such as *Streptococcus* and *Staphylococcus*, within the lung environment monopolizes resources, releases antimicrobial and proapoptotic factors that remove beneficial commensals, and weakens the immune defenses. This creates a vicious cycle in which the loss of diversity allows further pathogen expansion, ultimately leading to a pathogen-dominated environment that actively fuels the progression of IPF.

Immune systems under siege: the molecular mechanisms of microbial pathogenesis

The lung microbiome plays a dynamic and pivotal role in IPF, going far beyond mere colonization. It engages in complex interactions with both the innate and adaptive immune systems, actively shaping the lung's inflammatory environment in IPF [39,40]. These intricate relationships underscore that microbial communities are not just passive residents but active participants in the

disease process, profoundly influencing its progression. Several key pathways have been identified (Figure 2).

Th17 pathway activation and beyond: microbiome-driven immune dysregulation

Dysregulated commensal microbiota harness the host **Th17 immune cells**. Preclinical studies have demonstrated that the lung microbiota release outer membrane vesicles that activate Toll-like receptor-MyD88 pathways. This leads to the production of **IL-17B**, a potent fibrogenic cytokine that accelerates collagen deposition and tissue remodeling characteristic of IPF [20]. Remarkably, this inflammatory response persists even after the initial microbial trigger has been cleared, suggesting that microbiome-driven immune reprogramming may be a long-term driver of lung fibrosis.

Beyond Th17, IPF involves additional immune alterations that may intersect with microbial signals, including aberrant M2 macrophage polarization, Treg dysfunction that compromises peripheral tolerance, altered B-cell responses and autoantibody production, complement activation that contributes to epithelial injury, and neutrophil dysregulation that correlates with disease severity [41–44]. Whether dysbiosis directly drives these immune perturbations or merely amplifies pre-existing defects remains an important question for future integrated microbiome–immune profiling studies.

Innate immune receptor signaling

Innate immune receptor signaling offers another pathway through which lung dysbiosis impacts IPF outcomes. Elevated levels of *Streptococcus* in the lungs are associated with increased NOD-like receptor signaling in peripheral blood, suggesting that local microbial changes can trigger systemic immune activation [45]. Several innate immune pathways are associated with lung microbial features and relate to progression-free survival. This suggests exhaustion or

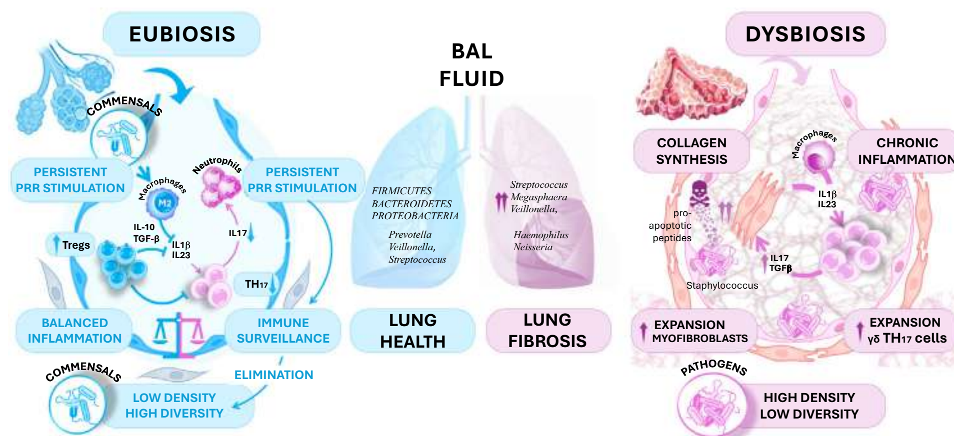

Figure 2. Microbial dysbiosis amplifies chronic inflammation and fibrotic remodeling in the lung. In healthy lungs (eubiosis), a low-density, diverse microbiota dominated by oral commensals (*Prevotella*, *Veillonella*, and *Streptococcus*) sustains a balanced pattern-recognition receptor (PRR) signaling pattern that promotes immune tolerance through regulatory T cells and M2 macrophages secreting IL-10 and TGF-β, thereby preserving epithelial integrity. Conversely, dysbiosis, characterized by reduced diversity and increased bacterial burden, features the expansion of pathobionts (*Streptococcus*, *Megasphaera*, *Haemophilus*, and *Neisseria*). Persistent PRR activation drives neutrophil recruitment and TH17/γδ T-cell polarization with IL-17 production, establishing a self-sustaining cycle of epithelial injury, myofibroblast expansion, and collagen deposition. Bacterial products, including proapoptotic peptides from *Staphylococcus*, further amplify fibroblast activation and extracellular matrix accumulation, perpetuating fibrotic remodeling. IL: interleukin.

CellPress

dysfunction of host defense mechanisms overwhelmed by persistent microbial stimulation [46]. This immune exhaustion may create a permissive environment for further microbial growth and repetitive alveolar injury in IPF.

The role of host genetic susceptibility in modulating microbiome–immune responses adds another layer of complexity to IPF development. The Toll-interacting protein (TOLLIP) polymorphism rs5743890 is associated with distinct lung microbial communities [47,48], exemplifying these gene–microbiome interactions that partly explain the heterogeneous clinical presentations among IPF patients.

Beyond IPF: microbiome signatures across the ILD spectrum

While IPF exhibits the most robust associations between the microbiome and outcomes, other ILDs display distinct signatures, highlighting the diversity of host–microbe interactions in lung disease (Box 3). However, extrapolating findings from IPF to the broader ILD spectrum warrants caution, as each entity is shaped by unique pathophysiological mechanisms and therapeutic exposures.

Hypersensitivity pneumonitis harbors environmental microbes with a lower bacterial burden that does not predict mortality, in sharp contrast to IPF. Similarly, post-COVID fibrosis maintains microbiome resilience, resembling that of healthy controls, despite architectural changes. The preservation of microbial diversity in post-COVID fibrosis challenges fibrosis-centric explanations for dysbiosis, demonstrating that fibrosis alone does not drive dysbiosis. The mechanisms underlying this resilience remain incompletely understood but may reflect the acute rather than chronic nature of the initial insult, preserved mucociliary clearance in nonhoneycombing fibrosis, and the

Box 3. Microbiome signatures beyond idiopathic pulmonary fibrosis

Other ILDs show distinct microbial signatures that reflect divergent pathogenic mechanisms.

One such disease, ‘hypersensitivity pneumonitis’ (HP), is characterized by an exaggerated immune response in which persistent inhalation of microbial antigens directly leads to chronic hypersensitivity and fibrosis [49–51]. Although HP shares some histopathological features with IPF, its microbiome differs significantly. Notably, fibrotic HP patients exhibit lower bacterial burdens than IPF patients, and, critically, this bacterial burden does not predict mortality in this population [14]. These fundamental differences suggest that although both diseases culminate in pulmonary fibrosis, their underlying pathogenic mechanisms and microbiome contributions differ substantially [52].

Several environmental microbes, including *Thermoactinomyces* and *Acinetobacter* spp., have been identified as potential causative agents in HP [50]. Increased similarity between environmental and lung tissue microbial communities has been observed in occupational lung disease, providing proof of concept that environmental microbiota can directly influence lung microbial composition [53]. This emerging concept of environmental microbiota offers a promising pathway for microbiome-targeted therapies, although data on the role of the lung microbiome in HP remain limited.

Same lung fibrosis, different microbiota: COVID-19’s surprising lesson

The coronavirus disease 2019 (COVID-19) pandemic has further illuminated the relationship between viral infections and lung fibrosis. Viral infections are established triggers of TGF-β, which activates fibroblasts and promotes excessive matrix deposition, thereby contributing to a cycle of injury, immunosuppression, and persistent infection. This vicious cycle illustrates why IPF patients are at heightened risk for severe outcomes following COVID-19 [54].

Interestingly, the post-COVID pulmonary fibrosis landscape does not recapitulate the IPF dysbiosis pattern. For instance, BAL fluid from post-COVID patients shows increased α-diversity and higher levels of *Streptococcus*, resembling healthier microbial profiles rather than those characteristic of IPF [55]. This distinction suggests that microbial imbalances in chronic fibrosis are not merely a result of lung damage but reflect disease-specific host–microbe interactions.

The persistence of TGF-β signaling in IPF likely exerts selective pressures that favor specific microbial communities. Thus, microbial resilience, or its absence, may be crucial in determining whether lung repair succeeds or results in chronic scarring. Ultimately, these findings indicate that fibrosis alone cannot predict microbial composition; rather, interactions among immune responses, tissue remodeling, and environmental factors are pivotal in shaping lung microbial communities, opening new avenues for research and personalized therapies.

absence of the progressive epithelial dysfunction characteristic of IPF. Additional contributing factors may include the lack of chronic epithelial senescence, transient TGF-β signaling, and effective immune resolution following viral injury. Together, these contrasting patterns suggest that IPF-associated dysbiosis reflects disease-specific host–microbe interactions rather than architectural remodeling *per se*.

Connective tissue diseases (CTDs) are a major group of autoimmune disorders in which the immune system mistakenly attacks self-antigens, resulting in persistent inflammation. The lungs, with their extensive vascular network and embedded connective tissue, are particularly vulnerable to this immune-mediated damage. If left unchecked, such chronic inflammation can result in respiratory failure and death [56,57]. Beyond genetic susceptibility and environmental exposures, increasing evidence suggests that the microbiome plays a key role in linking environmental factors to autoimmunity. A primary mechanism underlying this connection is molecular and structural mimicry, in which microbial peptides share antigenic similarity with host proteins, triggering crossreactive immune responses that inadvertently target self-tissues and contribute to autoimmune lung injury [58].

Early research in rheumatoid arthritis patients has shown that treatment-naïve patients harbor a less diverse microbiome, often enriched with oral pathogens such as *Treponema* and *Porphyromonas* [59]. Similarly, analysis of BAL fluid from patients with dermatomyositis or rheumatoid arthritis-associated ILD reveals elevated levels of Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria compared to healthy individuals [60]. Interestingly, while many CTDs share overlapping microbial changes and inflammatory pathways, each autoimmune condition appears to display a unique microbial signature. This disease-specific microbiota may not only reflect differences in immune dysregulation but also drive disease phenotype, influencing the balance between immune tolerance, inflammation, and fibrosis.

A critical interpretive limitation in CTD–ILD microbiome studies is the confounding effect of immunosuppressive therapies. Most patients with CTD–ILD receive corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologics, which profoundly alter microbial composition, immune tone, and epithelial barrier function, independently of the underlying autoimmune disease. Consequently, microbial signatures observed in CTD–ILD may reflect treatment effects or systemic immune dysregulation rather than primary drivers of fibrosis, as truly treatment-naïve CTD–ILD cohorts are rare. Longitudinal studies incorporating sampling before and after the initiation of immunosuppression will be essential to disentangle these confounders. Ultimately, a deeper understanding of how microbial signatures affect local immune networks in CTD–ILD could help identify microbiome-informed biomarkers and therapeutic strategies aimed at restoring the microbial–immune balance rather than just suppressing inflammation.

The oral–lung axis: gateway to disease

The anatomical continuity between the oropharynx and the lower respiratory tract provides a direct ‘runaway’ pathway for microbial translocation (Figure 3). In healthy individuals, oral and lung microbial communities significantly overlap, with microbial biomass progressively decreasing from the oropharynx toward the lower lobes [61–64]. This connection operates through subclinical microaspiration, a physiological process that occurs in all individuals during sleep and remains harmless under normal conditions.

The *Streptococcus* paradox: from oral commensal to lung pathobiont

The genus *Streptococcus* illustrates a central paradox in lung microbiome research: the same taxonomic group can exert protective or detrimental effects depending on anatomical site,

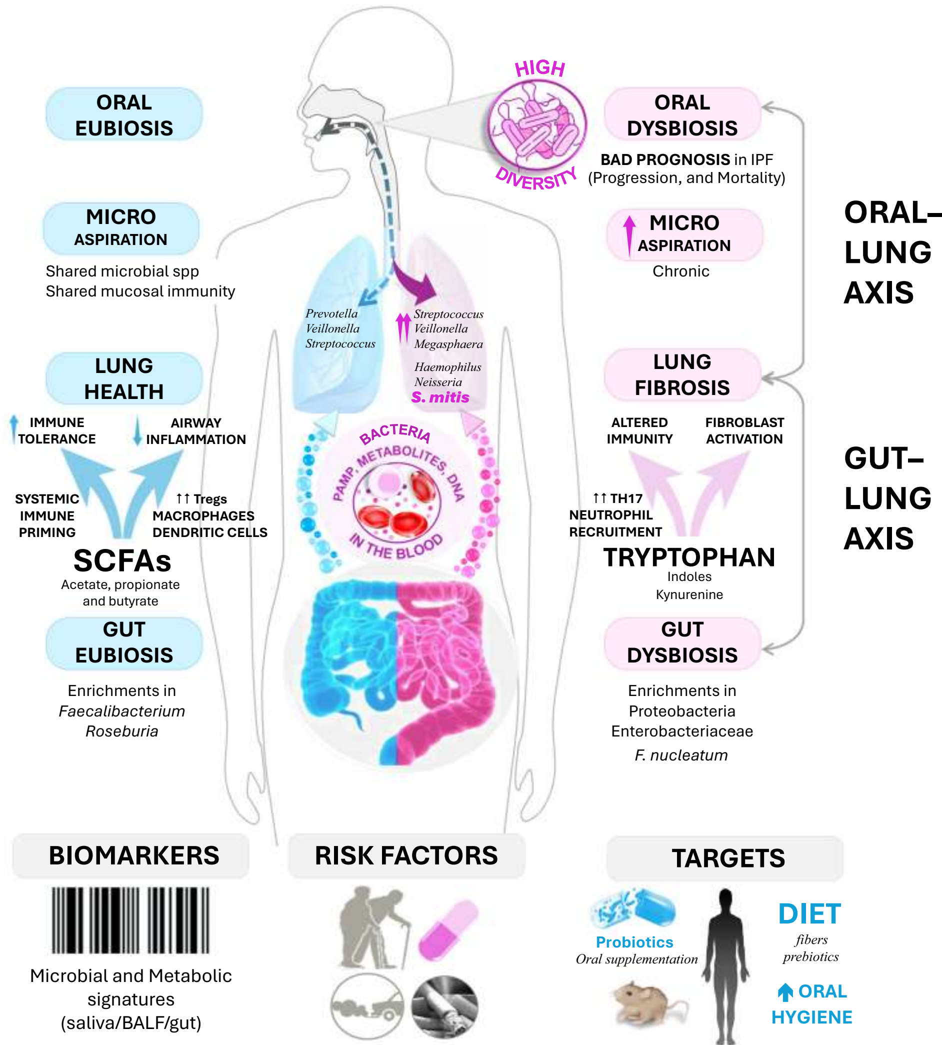

Figure 3. Oral–gut–lung axis in lung fibrosis. Bidirectional communication between the oral, gut, and lung microbiomes modulates pulmonary immunity and fibrogenesis. Oral–lung axis: In health, a balanced oral microbiome supports immune tolerance through the controlled microaspiration of commensals, such as *Prevotella* and *Veillonella*. In contrast, dysbiosis is characterized by the overrepresentation of *S. mitis*, *Haemophilus*, and *Neisseria* in the lower airways, which correlates with the progression of idiopathic pulmonary fibrosis (IPF) through TH17 activation, neutrophilic inflammation, and fibroblast proliferation. Gut–lung axis: Intestinal eubiosis enriched in *Faecalibacterium* and *Roseburia* supports anti-inflammatory short-chain fatty acid (SCFA) production (acetate, propionate, and butyrate), which enhances regulatory T-cell (Treg) function and dampens systemic inflammation. Conversely, gut dysbiosis, characterized by the expansion of Proteobacteria or Enterobacteriaceae, diverts tryptophan metabolism toward the proinflammatory kynurenine pathway, thereby amplifying neutrophilic inflammation. Systemic integration: circulating microbial metabolites, pathogen-associated molecular patterns (PAMPs), and bacterial DNA establish molecular crosstalk between mucosal sites. Clinical implications: Microbial signatures detected in saliva, bronchoalveolar lavage (BAL) fluid, or stool represent promising biomarkers, while therapeutic strategies aimed at microbiome restoration (probiotics, dietary fiber, oral hygiene) may enhance pulmonary resilience. Collectively, these interconnected pathways position the microbiome as both a driver and a therapeutic target in fibrotic lung disease.

species identity, and host context. In health, occasional microaspiration introduces only trace amounts of oral bacteria, which are rapidly cleared; this may even educate mucosal immunity and help maintain tolerance. The COMET trial has shown that the abundance and composition

of oral microbiota have significant implications for disease progression and outcomes [12]. Notably, a higher abundance of *Streptococcus* (especially *Streptococcus mitis*) was positively associated with better lung function and improved survival [32,34].

Understanding the *S. mitis* pathogenicity paradox

How can *S. mitis* appear protective in the oral niche, yet be associated with adverse outcomes in the IPF lung? Preclinical models demonstrate that in the oral niche, *S. mitis* functions as a commensal that not only maintains immune tolerance programs (e.g., IL-10-producing Tregs, secretory IgA) but also produces hydrogen peroxide and bacteriocins that suppress the overgrowth of pathogenic *Pseudomonas* or *Haemophilus*, thereby protecting the lung from inflammatory dysbiosis [65,66].

In contrast, in IPF, epithelial injury and altered mucociliary clearance increase both the frequency and volume of microaspiration events. This transforms a low-dose, tolerogenic exposure into a persistent danger signal, overwhelming clearance mechanisms and leading to sustained type I IFN, TLR2/TLR4, and Th17 pathways that promote chronic lung inflammation and fibroblast activation [40,67,68]. To capture this paradox, we propose a 'two-hit' model in which disease progression reflects not simply increased microbial exposure but also a failure of host regulatory mechanisms to respond appropriately to it. This includes impaired epithelial barrier integrity, altered macrophage polarization, regulatory T-cell dysfunction, and deregulated PRR signaling thresholds. Neither factor alone is sufficient, but together, they drive proinflammatory pathology. We acknowledge that this framework remains partially speculative. Functional characterization of lung microbes *in situ* is still in its infancy, and definitive studies distinguishing the relative contributions of microbial dose from host immunoregulatory failure are lacking. The inability of the IPF lung to appropriately regulate responses to aspirated commensals represents a fundamental knowledge gap that must be addressed through integrated multiomics approaches, gnotobiotic models, and longitudinal human sampling. Addressing this knowledge gap will require bridging clinical observations of esophageal dysmotility, aspiration, and oropharyngeal dysfunction with the immunobiology of IPF and other ILDs [69,70].

Distant influencers: the gut–lung microbiome connection

At the other end, a bidirectional crosstalk between the gut microbiota and the lungs, termed the 'gut–lung axis', significantly influences the severity of ILD [6], particularly CTD-related ILD (CTD–ILD) (Figure 3). Emerging evidence suggests that the gut–lung axis may also contribute to alterations in the lung microbiome in IPF. Gut dysbiosis can influence pulmonary immunity through multiple mechanisms, including direct bacterial translocation from the gastrointestinal tract via the bloodstream or lymphatic system, microaspiration of gastric contents, and systemic effects mediated by circulating microbial metabolites such as short-chain fatty acids. Studies have demonstrated that manipulating the gut microbiota can modulate lung fibrosis severity in experimental models, highlighting the potential therapeutic relevance of targeting the gut–lung axis in IPF [71–75].

Gut microbial dysbiosis as a biomarker of CTD–ILD severity

Lung diseases, notably CTD–ILD (such as dermatomyositis, Sjögren's syndrome, or myositis-ILD), often coincide with reduced gut microbial diversity and an overgrowth of inflammatory *Proteobacteria* and *Streptococcus* [76–78]. These alterations in gut microbiota are correlated with lung disease severity. They are associated with periods of intestinal barrier dysfunction, which allow gut bacteria and lipopolysaccharides to enter the bloodstream, thereby exacerbating lung inflammation and fibrosis [79]. Conversely, the intestinal bacterium *Roseburia*, known for producing the anti-inflammatory compound butyrate, shows a protective effect against ILD,

Clinician's corner

Microbiome as a prognostic tool: bacterial burden and community composition in bronchoalveolar lavage (BAL) fluid are emerging biomarkers that independently predict mortality and disease progression in idiopathic pulmonary fibrosis, beyond traditional pulmonary function tests and imaging. Integrating microbiome profiling with pulmonary function tests and high-resolution computed tomography may enhance patient stratification and inform treatment decisions.

Dysbiosis patterns identify high-risk phenotypes: patients who show an increase in *Streptococcus*, *Staphylococcus*, or *Haemophilus* in BALfluid experience faster decline in lung function and a higher risk of acute exacerbations, whereas some oral commensals may have protective effects when confined to their native niches. Conversely, maintaining diverse commensal communities is associated with better outcomes, suggesting that the microbiome could be a therapeutic target.

Precision interventions require targeted therapeutic approaches: broad-spectrum antibiotic trials have failed to show clinical benefit, likely due to insufficient microbial suppression and collateral damage to protective commensals. Future strategies should focus on pathogen-selective interventions, including inhaled antimicrobials, bacteriophage therapy, or metabolite supplementation, guided by individual microbiome profiles.

Beyond the lung, extrapulmonary microbial communities deserve clinical attention. The oral–lung axis and gut–lung axis are emerging as modifiable disease triggers. Improving oral hygiene, managing gastroesophageal reflux and microaspiration, and implementing dietary interventions that promote a healthy gut microbiota may present therapeutic opportunities in interstitial lung disease management. Focusing on oral hygiene, esophageal dysmotility, and gut microbiome health could be key modifiable factors that influence pulmonary outcomes through the oral–lung and gut–lung axes.

revealing an inverse relationship with the condition [76]. The complexity deepens with rheumatoid arthritis-related ILD, where shifts are not limited to bacteria but also involve viral and fungal communities, highlighting complex multikingdom interactions that may drive disease progression [80,81].

From mice to mechanisms: a metabolite-driven gut–lung dialog in fibrosis

Evidence from murine models provides compelling proof of causality: Horizontal transfer of the gut microbiota via fecal microbiota transplantation or cohousing markedly reduces mortality in bleomycin-induced lung fibrosis [21,82,83]. Mechanistically, the gut microbiome regulates pulmonary homeostasis via diverse metabolites, particularly **short-chain fatty acids (SCFAs)**, such as acetate, propionate, and butyrate, which are fermentation products of dietary fibers. Once in the systemic circulation, SCFAs have broad immunomodulatory effects, including the differentiation of regulatory T cells (Treg cells), which help maintain immune tolerance and prevent excessive inflammation. Butyrate restrains excessive myelopoiesis by fostering a regulatory phenotype in myeloid progenitors and mature neutrophil populations by inhibiting histone deacetylase activity [84–89].

Conversely, lung fibrosis can also remodel the gut microbiota and its metabolic landscape [90]. In models of bleomycin- or silica-induced fibrosis, there are notable compositional shifts within intestinal communities, characterized by an overrepresentation of *Lachnospiraceae_NK4A136_group*, *Allobaculum*, *Alistipes*, and *Candidatus_Saccharimonas* [91]. These changes correlate with circulating L-tryptophan and its microbial derivatives, implicating a metabolite-mediated gut–lung dialog. The accumulation of tryptophan metabolites in serum and lung tissue amplifies inflammation and fibrogenesis. *In vitro*, tryptophan enhances cytokine release, neutrophil extracellular trap formation, and fibroblast activation through the mTOR pathway, defining a metabolite-driven gut–lung axis that fuels pulmonary fibrosis [91,92].

Concluding remarks and future perspectives

Recognition of the role of bacterial burden in IPF has highlighted the lung microbiome as a potential therapeutic target. However, early antibiotic trials have illustrated this translational challenge: while small retrospective analyses of cotrimoxazole or azithromycin suggested potential benefits [93,94], larger multicenter studies, such as CleanUP-IPF and EME-TIPAC, did not show improvements with broad-spectrum antibiotics [95,96]. A critical limitation of these trials was the absence of microbiome profiling, which precluded confirmation that the interventions meaningfully altered microbial communities. Given widespread antibiotic resistance among commensals [97,98] and insufficient dosing or penetration into fibrotic lung compartments, the interventions may not have achieved their intended microbiological target. Additional confounding factors include collateral damage to protective commensals [99,100], inadequate patient selection, and suboptimal timing of intervention. Without demonstrating actual microbial modulation, these negative results cannot mechanistically refute the involvement of the microbiome in IPF itself; they simply indicate that the specific interventions tested were ineffective. These repeated failures illustrate that the journey from mechanistic insight to effective clinical treatment has proven more complex than anticipated.

Despite these therapeutic hurdles, microbiome profiling holds immediate translational potential. The consistent link between bacterial burden and mortality across different IPF cohorts suggests that microbiome metrics could enhance current prognostic models, refining risk assessment and treatment decisions. Future studies that integrate airway, oral, and gut microbiota with metabolomic and immune profiling might reveal microbial–metabolic signatures predictive of disease progression or therapeutic response (see Outstanding questions).

Outstanding questions

Does microbial dysbiosis initiate fibrosis, or does progressive fibrosis create permissive niches that favor the lung microbiome to become pathogenic?

Can longitudinal microbiome profiling, integrated with metabolomic and immune signatures, predict individual disease trajectories and therapeutic responses with sufficient precision to guide personalized therapeutic decisions in specific interstitial lung disease subtypes?

What are the specific pathways through which oral and gut microbiota communicate with lung tissue? Do circulating microbial metabolites (e.g., short-chain fatty acids and tryptophan derivatives) directly modulate pulmonary inflammation and fibrosis, or do they act through systemic immune reprogramming?

Could bacterial toxins such as corisin and pneumolysin serve as actionable therapeutic targets? Do circulating levels of these peptides function as biomarkers for acute exacerbation risk or for monitoring treatment response?

Which precision interventions—ranging from targeted antimicrobials and probiotics to microbiota transplantation and postbiotic metabolites—can restore microbial–immune homeostasis without disrupting beneficial commensals? What are the optimal timing, delivery routes, and patient selection criteria for these approaches?

As we move from observation to intervention, rational microbiome-targeted therapies will require a fundamental shift in approach. Precision interventions that selectively eliminate pathogenic bacteria while preserving beneficial commensals may prove more effective than broad-spectrum antibiotics. Inhaled antibiotic formulations could modify microbial environments locally with minimal systemic impact, though no such precision antibiotic has yet been validated in IPF. One promising avenue involves targeting corisin, a proapoptotic peptide produced by dysbiotic microbiota, which exacerbates IPF by killing lung epithelial cells [28]. Preclinical studies have demonstrated that a monoclonal antibody can neutralize corisin's effects in mouse models, preventing acute exacerbations and reducing fibrosis, while also neutralizing toxic effects in BAL fluid from IPF patients [31]. This targeted immunotherapy against a microbial toxin implicated in epithelial injury represents an attractive strategy, but human trials have not yet begun.

Beyond antibiotics, microbiome-restoration strategies such as probiotics, postbiotics, microbial consortia, and metabolites offer additional therapeutic avenues. However, establishing and maintaining beneficial microorganisms in the fibrotic lung present unique challenges: the altered mucus composition, impaired mucociliary clearance, and proinflammatory microenvironment characteristic of IPF may prevent engraftment or shift probiotic strains toward pathogenic behavior. To date, no clinical trial has demonstrated successful colonization of the IPF lung with therapeutic microbiota, and the regulatory pathway for such living therapeutics remains uncertain.

The field stands at an 'inflection point'. We have moved from dismissing the lung as sterile to recognizing the microbiome's prognostic significance. Yet the challenge now is not recognizing the microbiome's therapeutic importance but determining how to safely and effectively harness it. This will require not only scientific innovation but also standardized methodologies, robust multicenter validation, and navigation of complex regulatory frameworks for microbiome-based therapeutics. The path forward demands tempered optimism: while the microbiome holds genuine promise, transforming this promise into validated clinical interventions will likely span decades rather than years (see Clinician's corner).

Acknowledgments

A.B. received a postdoctoral fellowship from ANR (IHU RespirERA). This work was supported by the French National Research Agency ['IHU RespirERA' France 2030 program # ANR-23-IAHU-0007; ANR-25-CE17-5302-02; IDEX reference (IDEX UCAJedi ANR-15-IDEX-01)] and 'Investments for the Future' LABEX SIGNALIFE (program reference # ANR-11-LABX-0028–01), as well as Cancéropôle PACA, Plan Cancer INSERM, and FHU OncoAge, Institut National du Cancer PL-Bio (INCa_18414). The funding organizations had no role in the design and conduct of the study.

Declaration of interests

P.H. has received honoraria for travel support and consulting/advisory roles from AstraZeneca, Roche, Bristol–Myers Squibb, Novartis, Pfizer, MSD, Qiagen, Thermo Fisher Scientific, Janssen, AbbVie, Biocartis, Pierre Fabre, Amgen, Bayer, and Sanofi, outside the submitted work. S.L. has received honoraria for congress and travel support, as well as scientific meeting and advisory role fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Sanofi, Stallergenes Greer, Viatris, and Zambon, outside the submitted work. The remaining authors (B.R., A.B., P.B., C.H.M., V.V-C., V.H., and B.M.) declare no conflicts of interest. The funders had no role in the study's design, the collection, analyses, or interpretation of data, the writing of the manuscript, or the decision to publish the results.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Grammarly in order to support the writing process and improve the language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

1. Maher, T.M. (2024) Interstitial lung disease: a review. *JAMA* 331, 1655–1665
2. Hilberg, O. *et al.* (2022) Epidemiology of interstitial lung diseases and their progressive-fibrosing behaviour in six European countries. *ERJ Open Res.* 8, 00597–02021
3. Dickson, R.P. *et al.* (2016) The microbiome and the respiratory tract. *Annu. Rev. Physiol.* 78, 481–504
4. Lipinski, J.H. *et al.* (2020) The evolving role of the lung microbiome in pulmonary fibrosis. *Am. J. Physiol. Lung Cell Mol. Physiol.* 319, L675–L682
5. Eisenhofer, R. *et al.* (2019) Contamination in low microbial biomass microbiome studies: issues and recommendations. *Trends Microbiol.* 27, 105–117
6. Belaid, A. *et al.* (2024) Impact of the lung microbiota on development and progression of lung cancer. *Cancers* 16, 3342
7. Guillot, N. *et al.* (2023) Manipulating the gut and tumor microbiota for immune checkpoint inhibitor therapy: from dream to reality. *Trends Mol. Med.* 29, 897–911
8. Molyneaux, P.L. *et al.* (2014) The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 190, 906–913
9. Sulaiman, I. *et al.* (2021) Functional lower airways genomic profiling of the microbiome to capture active microbial metabolism. *Eur. Respir. J.* 58, 2003434
10. Zinter, M.S. *et al.* (2021) The pulmonary metatranscriptome prior to pediatric HCT identifies post-HCT lung injury. *Blood* 137, 1679–1689
11. Takeuchi, S. *et al.* (2025) Metagenomic analysis of lung microbiome in patients with interstitial lung diseases and sarcoidosis: an experimental study. *Heal. Sci. Rep.* 8, e70328
12. O'Dwyer, D.N. *et al.* (2019) Lung microbiota contribute to pulmonary inflammation and disease progression in pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 199, 1127–1138
13. Invernizzi, R. *et al.* (2020) Bacterial burden in the lower airways predicts disease progression in idiopathic pulmonary fibrosis and is independent of radiological disease extent. *Eur. Respir. J.* 55, 1901519
14. Invernizzi, R. *et al.* (2021) The respiratory microbiome in chronic hypersensitivity pneumonitis is distinct from that of idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 203, 339–347
15. Molyneaux, P.L. *et al.* (2017) Changes in the respiratory microbiome during acute exacerbations of idiopathic pulmonary fibrosis. *Respir. Res.* 18, 29
16. Dickson, R.P. *et al.* (2020) Making the case for causality: what role do lung microbiota play in idiopathic pulmonary fibrosis? *Eur. Respir. J.* 55, 2000318
17. Corander, J. *et al.* (2022) Causal discovery for the microbiome. *Lancet Microbe* 3, e881–e887
18. Dickson, R.P. *et al.* (2019) Radiographic honeycombing and altered lung microbiota in patients with idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 200, 1544–1547
19. Jacob, J. *et al.* (2020) Serial CT analysis in idiopathic pulmonary fibrosis: comparison of visual features that determine patient outcome. *Thorax* 75, 648–654
20. Yang, D. *et al.* (2019) Dysregulated lung commensal bacteria drive interleukin-17B production to promote pulmonary fibrosis through their outer membrane vesicles. *Immunity* 50, 692–706.e7
21. Gurczynski, S.J. *et al.* (2023) Horizontal transmission of gut microbiota attenuates mortality in lung fibrosis. *JCI Insight* 9, e164572
22. Ivanov, I.I. *et al.* (2009) Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell* 139, 485–498
23. Bry, L. *et al.* (1996) A model of host-microbial interactions in an open mammalian ecosystem. *Science* 273, 1380–1383
24. Cash, H.L. *et al.* (2006) Symbiotic bacteria direct expression of an intestinal bactericidal lectin. *Science* 313, 1126–1130
25. Bouskra, D. *et al.* (2008) Lymphoid tissue genesis induced by commensals through NOD1 regulates intestinal homeostasis. *Nature* 456, 507–510
26. Kitsios, G.D. *et al.* (2018) Microbiome in lung explants of idiopathic pulmonary fibrosis: a case-control study in patients with end-stage fibrosis. *Thorax* 73, 481–484
27. Valenzi, E. *et al.* (2021) Topographic heterogeneity of lung microbiota in end-stage idiopathic pulmonary fibrosis: the Microbiome in Lung Explants-2 (MiLEs-2) study. *Thorax* 76, 239–247
28. D'Alessandro-Gabazza, C.N. *et al.* (2020) A *Staphylococcus* pro-apoptotic peptide induces acute exacerbation of pulmonary fibrosis. *Nat. Commun.* 11, 1539
29. D'Alessandro-Gabazza, C.N. *et al.* (2018) Identification of halophilic microbes in lung fibrotic tissue by oligotyping. *Front. Microbiol.* 9, 1892
30. Frank, J.A. and Matthay, M.A. (2014) TGF-β and lung fluid balance in ARDS. *Proc. Natl. Acad. Sci. U. S. A.* 111, 885–886
31. D'Alessandro-Gabazza, C.N. *et al.* (2022) Inhibition of lung microbiota-derived proapoptotic peptides ameliorates acute exacerbation of pulmonary fibrosis. *Nat. Commun.* 13, 1558
32. Han, M.L.K. *et al.* (2014) Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study. *Lancet Respir. Med.* 2, 548–556
33. Knippenberg, S. *et al.* (2015) *Streptococcus pneumoniae* triggers progression of pulmonary fibrosis through pneumolysin. *Thorax* 70, 636–646
34. Musher, D.M. *et al.* (2020) Normal respiratory flora as a cause of community-acquired pneumonia. *Open Forum Infect. Dis.* 7, ofaa307
35. Mikhail, S.G. and O'dwyer, D.N. (2025) The lung microbiome in interstitial lung disease. *Breathe* 21, 240167
36. Takahashi, Y. *et al.* (2018) Impaired diversity of the lung microbiome predicts progression of idiopathic pulmonary fibrosis. *Respir. Res.* 19, 34
37. Lynch, S.V. and Pedersen, O. (2016) The human intestinal microbiome in health and disease. *N. Engl. J. Med.* 375, 2369–2379
38. Peled, J.U. *et al.* (2020) Microbiota as predictor of mortality in allogeneic hematopoietic-cell transplantation. *N. Engl. J. Med.* 382, 822–834
39. Segal, L.N. *et al.* (2013) Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation. *Microbiome* 1, 19
40. Dickson, R.P. *et al.* (2018) The lung microbiota of healthy mice are highly variable, cluster by environment, and reflect variation in baseline lung innate immunity. *Am. J. Respir. Crit. Care Med.* 198, 497–508
41. Shirai, Y. *et al.* (2025) Serum vesicle biomarkers reflect the disease activity of idiopathic pulmonary fibrosis. *J. Transl. Med.* 23, 1102
42. Mendoza, N. *et al.* (2023) Blood immunophenotypes of idiopathic pulmonary fibrosis: relationship with disease severity and progression. *Int. J. Mol. Sci.* 24, 13832
43. Kotsianidis, I. *et al.* (2009) Global impairment of $CD4^+CD25^+FOXP3^+$ regulatory T cells in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 179, 1121–1130
44. Yang, Y. *et al.* (2024) Role of transient receptor potential ankyrin 1 in idiopathic pulmonary fibrosis: modulation of M2 macrophage polarization. *Cell. Mol. Life Sci.* 81, 187
45. Huang, Y. *et al.* (2017) Microbes are associated with host innate immune response in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 196, 208–219
46. Molyneaux, P.L. *et al.* (2017) Host-microbial interactions in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 195, 1640–1650
47. Noth, I. *et al.* (2013) Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. *Lancet Respir. Med.* 1, 309–317
48. Lipinski, J.H. *et al.* (2022) Toll-interacting protein and altered lung microbiota in idiopathic pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 206, 224–227
49. Fernández Pérez, E.R. *et al.* (2013) Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest* 144, 1644–1651
50. Raghu, G. *et al.* (2020) Diagnosis of hypersensitivity pneumonitis in adults: an official ATS/JRS/ALAT clinical practice guideline. *Am. J. Respir. Crit. Care Med.* 202, E36–E69
51. Hamblin, M. *et al.* (2022) Diagnosis, course and management of hypersensitivity pneumonitis. *Eur. Respir. Rev.* 31, 210169

52. O'Dwyer, D.N. and Garantziotis, S. (2021) The lung microbiome in health, hypersensitivity pneumonitis, and idiopathic pulmonary fibrosis: a heavy bacterial burden to bear. *Am. J. Respir. Crit. Care Med.* 203, 281–283
53. Wu, B.G. *et al.* (2020) Evidence for environmental–human microbiota transfer at a manufacturing facility with novel work-related respiratory disease. *Am. J. Respir. Crit. Care Med.* 202, 1678–1688
54. Kim, B.-G. *et al.* (2025) Clinical impacts of COVID-19 on severe exacerbation and mortality in interstitial lung disease: prognosis 30 days after infection. *Korean J. Intern. Med.* 40, 634–644
55. Smith, D.J.F. *et al.* (2025) The respiratory microbiome in patients with post-COVID-19 residual lung abnormalities resembles that of healthy individuals and is distinct from idiopathic pulmonary fibrosis. *ERJ Open Res.* 11, 00826–02024
56. Wells, A.U. and Denton, C.P. (2014) Interstitial lung disease in connective tissue disease - mechanisms and management. *Nat. Rev. Rheumatol.* 10, 728–739
57. Spagnolo, P. *et al.* (2016) Connective tissue diseases, multimorbidity and the ageing lung. *Eur. Respir. J.* 47, 1535–1558
58. Kohm, A.P. *et al.* (2003) Mimicking the way to autoimmunity: an evolving theory of sequence and structural homology. *Trends Microbiol.* 11, 101–105
59. Scher, J.U. *et al.* (2016) The lung microbiota in early rheumatoid arthritis and autoimmunity. *Microbiome* 4, 60
60. Lou, Y. *et al.* (2022) The composition of the lung microbiome differs between patients with dermatomyositis and rheumatoid arthritis associated with interstitial lung disease. *FEBS Open Bio* 12, 258–269
61. Hilty, M. *et al.* (2010) Disordered microbial communities in asthmatic airways. *PLoS One* 5, e8578
62. Charlson, E.S. *et al.* (2011) Topographical continuity of bacterial populations in the healthy human respiratory tract. *Am. J. Respir. Crit. Care Med.* 184, 957–963
63. Dickson, R.P. *et al.* (2017) Bacterial topography of the healthy human lower respiratory tract. *mBio* 8, e02287
64. Bassis, C.M. *et al.* (2015) Analysis of the upper respiratory tract microbiotas as the source of the lung and gastric microbiotas in healthy individuals. *mBio* 6, e00037
65. Tony-Odigie, A. *et al.* (2022) Commensal bacteria in the cystic fibrosis airway microbiome reduce P. aeruginosa induced inflammation. *Front. Cell. Infect. Microbiol.* 12, 824101
66. Borralho, J. *et al.* (2025) Inhibition of pneumococcal growth and biofilm formation by human isolates of *Streptococcus mitis* and *Streptococcus oralis*. *Appl. Environ. Microbiol.* 91, e0133624
67. Wu, B.G. *et al.* (2021) Episodic aspiration with oral commensals induces a MyD88-dependent, pulmonary T-helper cell type 17 response that mitigates susceptibility to *Streptococcus pneumoniae*. *Am. J. Respir. Crit. Care Med.* 203, 1099–1111
68. Wilson, M.S. *et al.* (2010) Bleomycin and IL-1β-mediated pulmonary fibrosis is IL-17A dependent. *J. Exp. Med.* 207, 535–552
69. Alamer, A. *et al.* (2022) Oropharyngeal swallowing physiology and safety in patients with idiopathic pulmonary fibrosis: a consecutive descriptive case series. *BMC Pulm. Med.* 22, 422
70. Ward, C. *et al.* (2024) Integrating aerodigestive investigations in progressive pulmonary fibrosis. *Am. J. Respir. Crit. Care Med.* 210, 530
71. Schuijt, T.J. *et al.* (2016) The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia. *Gut* 65, 575–583
72. Yang, J. *et al.* (2025) Lung-gut axis, intestinal microbiota, and pulmonary fibrosis: mechanisms and therapeutic potential. *Front. Microbiol.* 16, 1711299
73. Yu, X. *et al.* (2025) Respiratory diseases and the gut microbiota: an updated review. *Front. Cell. Infect. Microbiol.* 15, 1629005
74. Liu, C. *et al.* (2022) Effect of invasive mechanical ventilation on the diversity of the pulmonary microbiota. *Crit. Care* 26, 252
75. Gao, H. *et al.* (2025) Whole genome comparisons reveal gut-to-lung translocation of *Escherichia coli* and *Burkholderia cenocepacia* in two cases of ventilator-associated pneumonia in ICU patients. *Respir. Res.* 26, 178
76. Liang, X. *et al.* (2023) Gut microbiota dysbiosis characterized by abnormal elevation of *Lactobacillus* in patients with immune-mediated necrotizing myopathy. *Front. Cell. Infect. Microbiol.* 13, 1243512
77. Jia, X. *et al.* (2023) Compositional and functional aberrance of the gut microbiota in treatment-naïve patients with primary Sjögren's syndrome. *J. Autoimmun.* 141, 103050
78. Bae, S.S. *et al.* (2022) Altered gut microbiome in patients with dermatomyositis. *ACR Open Rheumatol.* 4, 658–670
79. Dickson, R.P. *et al.* (2016) Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. *Nat. Microbiol.* 1, 16113
80. Xing, Y. *et al.* (2024) Multikingdom characterization of gut microbiota in patients with rheumatoid arthritis and rheumatoid arthritis-associated interstitial lung disease. *J. Med. Virol.* 96, e29781
81. Zhong, X. *et al.* (2025) Alterations in gut microbiota in rheumatoid arthritis patients with interstitial lung disease: a comparative study. *Hum. Immunol.* 86, 111239
82. Yoon, Y.M. *et al.* (2022) Gut microbiota modulates bleomycin-induced acute lung injury response in mice. *Respir. Res.* 23, 337
83. Chioma, O.S. *et al.* (2022) Gut microbiota modulates lung fibrosis severity following acute lung injury in mice. *Commun. Biol.* 5, 1401
84. Deshmukh, H.S. *et al.* (2014) The microbiota regulates neutrophil homeostasis and host resistance to *Escherichia coli* K1 sepsis in neonatal mice. *Nat. Med.* 20, 524–530
85. Ichinohe, T. *et al.* (2011) Microbiota regulates immune defense against respiratory tract influenza a virus infection. *Proc. Natl. Acad. Sci. U. S. A.* 108, 5354–5359
86. Trompette, A. *et al.* (2018) Dietary fiber confers protection against flu by shaping $Ly6c^-$ patrolling monocyte hematopoiesis and $CD8^+$ T cell metabolism. *Immunity* 48, 992–1005.e8
87. Wypych, T.P. *et al.* (2021) Microbial metabolism of L-tyrosine protects against allergic airway inflammation. *Nat. Immunol.* 22, 279–286
88. Markey, K.A. *et al.* (2020) The microbe-derived short-chain fatty acids butyrate and propionate are associated with protection from chronic GVHD. *Blood* 136, 130–136
89. Huang, Y. *et al.* (2018) S1P-dependent interorgan trafficking of group 2 innate lymphoid cells supports host defense. *Science* 359, 114–119
90. Gong, G.C. *et al.* (2021) Pulmonary fibrosis alters gut microbiota and associated metabolites in mice: an integrated 16S and metabolomics analysis. *Life Sci.* 264, 118616
91. Li, J. *et al.* (2024) Roles of gut microbiome-associated metabolites in pulmonary fibrosis by integrated analysis. *NPJ Biofilms Microbiomes* 10, 154
92. Zheng, H. *et al.* (2025) Metabolic dysregulation in pulmonary fibrosis: insights into amino acid contributions and therapeutic potential. *Cell Death Discov.* 11, 411
93. Shulgina, L. *et al.* (2013) Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. *Thorax* 68, 155–162
94. Macaluso, C. *et al.* (2019) The potential impact of azithromycin in idiopathic pulmonary fibrosis. *Eur. Respir. J.* 53, 1800628
95. Martinez, F.J. *et al.* (2021) Effect of antimicrobial therapy on respiratory hospitalization or death in adults with idiopathic pulmonary fibrosis: the cleanUP-IPF randomized clinical trial. *JAMA* 325, 1841–1851
96. Wilson, A.M. *et al.* (2020) Effect of co-trimoxazole (trimethoprim-sulfamethoxazole) vs placebo on death, lung transplant, or hospital admission in patients with moderate and severe idiopathic pulmonary fibrosis: the EME-TIPAC randomized clinical trial. *JAMA* 324, 2282–2291
97. Gjonbalaj, M. *et al.* (2020) Antibiotic degradation by commensal microbes shields pathogens. *Infect. Immun.* 88, e00012
98. Nji, E. *et al.* (2021) High prevalence of antibiotic resistance in commensal *Escherichia coli* from healthy human sources in community settings. *Sci. Rep.* 11, 3372
99. Segal, L.N. *et al.* (2017) Randomised, double-blind, placebo-controlled trial with azithromycin selects for anti-inflammatory microbial metabolites in the emphysematous lung. *Thorax* 72, 13–22
100. Spence, C.D. *et al.* (2020) Influence of azithromycin and allograft rejection on the post–lung transplant microbiota. *J. Heart Lung Transplant.* 39, 176–183