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The microbiome in interstitial lung disease: from pathogenesis to treatment target

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Abstract

Purpose of Review—This review summarizes current knowledge of the role of the lung microbiome in interstitial lung disease and poses considerations of the microbiome as a therapeutic target.

Recent Findings—While historically considered sterile, bacterial communities have now been well documented in lungs in health and disease. Studies in idiopathic pulmonary fibrosis (IPF) suggest that increased bacterial burden and/or abundance of potentially pathogenic bacteria may drive disease progression, acute exacerbations, and mortality. More recent work has highlighted the interaction between the lung microbiome and the innate immune system in IPF, strengthening the argument for the role of both host and environment interaction in disease pathogenesis. In support of this, studies of interstitial lung diseases other than IPF suggest that it may be the host immune response which shapes the microbiome in these diseases. Some clinical and mouse model data also suggest that the lung microbiome may represent a therapeutic target, via antibiotic administration, immunization against pathogenic organisms, or treatment directed at gastroesophageal reflux.

Summary—Evidence suggests that the lung microbiome may serve as a prognostic biomarker, a therapeutic target, or provide an explanation for disease pathogenesis in IPF.

Keywords

Idiopathic pulmonary fibrosis; interstitial lung disease; microbiome; infection

Introduction

Interstitial lung diseases (ILDs) are a heterogeneous group of disorders with manifestations including dyspnea, hypoxia, cough, impaired pulmonary function, and various patterns of inflammation and fibrosis evident on radiologic or histopathologic evaluation of the lung.

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Conflicts of Interest

The remaining authors have no conflicts of interest.

While some ILDs are associated with an underlying systemic condition, such as rheumatoid arthritis or dermatomyositis, others are idiopathic and without a recognized driver of disease initiation or progression.(1) Microbes, including viruses,(2) bacteria,(3) and environmental fungi(4) have long been hypothesized to play a role in the pathogenesis of ILDs. Culture-dependent microbiological techniques have, to date, limited most researchers to focus on potential viral triggers in ILDs. However, advances in modern molecular sequencing technology over the past decade have allowed a more systematic study of the role of bacterial communities, or the “microbiome”, in lung health and disease, using culture independent approaches.

Evidence now suggests that increased bacterial burden and/or abundance of potentially pathogenic bacteria may drive disease progression, acute exacerbations, and mortality in idiopathic pulmonary fibrosis (IPF).(5–7) These observations, along with studies suggesting that antibiotic administration or immunization against pathogenic organisms may improve IPF outcomes,(8, 9) have created enthusiasm for evaluation of the lung microbiome as a therapeutic target. While most research to date has focused on IPF specifically, we are also now beginning to understand the composition of the lung microbiome in other ILDs. In those ILDs associated with immune system activation (i.e. connective tissue disease associated ILD or hypersensitivity pneumonitis), a different role for the lung microbiome may emerge, shaped by interaction of the host immune system with the local environment. This review article summarizes what is known about the lung microbiome in ILDs, and poses considerations of the microbiome as a therapeutic target.

The human airway contains a complex and dynamic microbiota

Modern methods of high-throughput molecular analysis have allowed for efficient culture-independent study of microbial contents in biologic samples. The gene for the variable 16S region of bacterial ribosomal RNA (rRNA) is selectively amplified and sequenced. Sequences are then grouped based on genetic similarity into operational taxonomic units (OTUs), with individual species identified by referencing a database.(10, 11) The bacterial community composition at various body sites is referred to as the microbiome.

Healthy lungs have historically been described as sterile, but use of modern sequencing methods has revealed a complex and dynamic microbiota in the respiratory tract. Bacterial communities in the lung appear to immigrate from the mouth,(12, 13) most commonly via microaspiration but also by direct dispersal along the mucosa.(14) The quantity and composition of the microbiome is influenced by rate of immigration and emigration via mucociliary clearance or host defense mechanisms, with local growth factors contributing very little to microbiome composition in healthy lungs.(15)

An altered lung microbiome predicts disease progression in IPF

It is believed that an impaired wound healing response in genetically susceptible individuals results in the progressive architectural distortion of the lung in IPF.(16) The “wound” initiating the aberrant healing response remains unclear, with environmental exposures (including cigarette smoking and industrial dusts), gastroesophageal reflux (GER), and

microbial agents hypothesized to contribute.(17) Lending support to the idea that microbes specifically contribute to disease progression in IPF is the finding that immunosuppressive therapy significantly increases the risk of death and other adverse events.(18)

The contribution of viral infections, including hepatitis C virus, transfusion transmitted virus, and human herpes virus, have been extensively studied, but with conflicting results across studies leading to doubt about their importance in disease pathogenesis.(19) Human herpes viruses (including Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and human herpes virus-7 and -8) have been identified in the lung tissue of a greater proportion of IPF patients as compared to controls,(2) and similar viruses enhance fibrosis in animal models.(19) These data are confounded by the high rate of receipt of immunosuppressive drugs in IPF patients, but could suggest a role of viruses as co-factors driving fibrosis progression.

The incorrectly held doctrine of lung sterility outside of clinical infection meant historically little work has evaluated the role of bacteria in IPF. However, recent research has characterized the lung microbiome in stable IPF, and linked microbial composition and bacterial burden with disease outcomes. Han and colleagues(5) evaluated the lung microbiome in IPF patients enrolled in the Correlating Outcomes with biochemical Markers to Estimate Time-progression (COMET)-IPF study. *Prevotella*, *Veillonella*, and *Cronobacter* species (spp.) were the most prevalent and abundant OTUs across this IPF cohort. After adjusting for age, sex, smoking status, GER, baseline pulmonary function and 6-minute walk desaturation status, having a specific *Streptococcus* or *Staphylococcus* OTU present with relative abundance above a specified threshold was associated with a clinically significant reduction in progression-free survival time. Of note, one or both OTUs were identified in less than half of the cohort, making it unlikely that these organisms completely explain disease pathogenesis.(5) The finding that potentially pathogenic organisms (here, *Streptococcus* and *Staphylococcus* sp.) are associated with increased risk of disease progression in humans is in line with the findings in two separate mouse models, where infection with *Streptococcus pneumoniae* results in exacerbation of existing lung fibrosis.(8)

Molyneaux and colleagues(7) prospectively enrolled IPF patients, chronic obstructive pulmonary disease (COPD) patients, and normal controls, comparing microbial composition in bronchoalveolar lavage fluid. IPF patients had significantly higher bacterial burden compared to COPD and healthy controls. While the most abundant species in both IPF and combined controls were *Streptococcus*, *Prevotella*, and *Veillonella* spp., IPF patients had significantly less diverse bacterial communities, and were more likely to harbor potentially pathogenic *Haemophilus*, *Neisseria* and *Streptococcus* spp. compared to controls. Among IPF patients, having a higher bacterial load was associated with a significantly reduced progression-free survival time compared to having a relatively lower bacterial load, an effect independent of age and smoking status. Unlike the results of Han and colleagues, no specific organism was associated with increased risk of disease progression. Interestingly, IPF patients harboring a *MUC5B* minor allele genotype, previously associated with increased risk of developing IPF and playing a role in mucociliary clearance,(20, 21) had significantly lower bacterial burden compared to IPF patients not harboring this genotype.(7) In a separate IPF cohort, Molyneaux and colleagues(6) found that IPF patients experiencing an

acute disease exacerbation had a bacterial burden which was four times higher compared to stable IPF controls matched by age, sex, smoking history, and baseline lung function. Exacerbated patients had relatively higher abundance of *Proteobacteria* sp., including significantly higher relative abundance of the potential pathogens *Campylobacter* and *Stenotrophomonas* spp., compared to controls.(6) Interestingly, *Campylobacter* is best known as a gastrointestinal pathogen. This finding supports the idea that GER may contribute to exacerbations in IPF.(17, 22) Initial work examining the fungal microbiome in IPF suggests there are no significant differences compared to healthy controls.(23) Figure 1 summarizes evidence for an association of lung microbiome alterations with disease progression in IPF.

Understanding interactions between host and lung microbiome in IPF

Recent studies have now begun to elucidate the link between host response to an altered lung microbiome and disease pathogenesis in IPF. Molyneaux and colleagues(24) evaluated bronchoalveolar lavage (BAL) microbiome measures, peripheral blood gene expression, and *MUC5B* and *TOLLIP* gene polymorphisms in IPF patients and matched healthy controls. Genotype polymorphisms were not associated with differences in gene expression profiles. Genes were grouped into five modules during analysis; three modules were associated with IPF and two were associated with healthy status. Over-expression of one IPF gene module was associated with death and physiologic disease progression, as well as elevated blood and BAL neutrophil markers, increased BAL bacterial burden, and decreased relative abundance of a specific *Neisseria* sp. This module was enriched with genes associated with host defense, response to bacterium, and immune response, including secretory leukocyte peptidase inhibitor (*SLPI*) and cathelicidin antimicrobial peptide (*CAMP*). Over-expression of *SLPI* was associated with worse survival. Over-expression of gene modules remained constant over time in IPF patients experiencing disease progression, and there were clear differences between those with rapidly progressive compared to stable disease.

Huang and colleagues(25) evaluated peripheral blood mononuclear cell gene expression, BAL microbiome features, and *in vitro* fibroblast responsiveness to stimulus in patients enrolled in the COMET-IPF study. Relative inhibition of 11 gene signaling pathways was associated with reduced progression-free survival time; 8 pathways involve immune/inflammatory response and pathogen infection, and 3 pathways involve components integral to the innate immune response including Toll-like receptors (TLRs), NOD-like receptors (NODs), and RIG 1-like receptors (RIG1) signaling pathways. Greater relative abundance of a *Streptococcal* OTU, previously associated with progressive IPF,(5) was negatively correlated with NODs expression. *TLR9* activation in myofibroblasts has been previously associated with rapid progression of IPF.(26) Huang et al(25) found *TLR9* expression to be positively correlated with *Staphylococcal* OTU1348, which also predicted *in vitro* fibroblast *TLR9* responsiveness (measured by >2-fold increase in alpha-SMA expression post-stimulation), suggesting that *TLR9* signaling may depend on lung microbial communities. A specific *Staphylococcal* OTU was also associated with accumulation of CXCR3+ CD8+ T cells which are involved in Th1 pathway signaling. Enrichment of this OTU in the lungs of IPF patients was previously associated with reduced progression-free survival.(5) It was also recently reported that administration of aerosolized inhaled interferon-gamma to IPF

patients for therapeutic purposes has little impact on lung microbiome composition, supporting the idea that the lung microbiome has an independent effect on the host immune milieu.(27) Taken together, these data lend further support for a link between lung microbiome alterations, an associated aberrant host response, and disease pathogenesis in IPF. Whether an abnormal microbiome triggers a host response, or an abnormal host response alters the microbiome remains unclear. Hypotheses and evidence for the role of bacteria in IPF pathogenesis are summarized in Figure 2.

The lung microbiome across ILDs

Several studies have evaluated the lung microbiome in ILDs other than IPF. The lung microbiome is proposed as a potential driver of injury and host response in IPF, with influx of organisms from the mouth (possibly originally sourced from the gastrointestinal tract) and altered mucociliary clearance with abnormal anatomy hypothesized to shape alterations to the microbiome. Conversely, limited evidence suggests that the immune system or other disease-specific host factors may have a greater role in shaping the lung microbiome in non-IPF ILD. Granulomatosis with polyangiitis (GPA) patients tend to harbor *Staphylococcus aureus* in the nasal passages, and culture of BAL fluid identified this pathogen in the lungs of over one-third of GPA patients compared to none of the concurrently studied IPF controls.(3) Further, BAL fluid supernatant from GPA patients acts as a growth factor for cultured *S. aureus*, while fluid from IPF patients and normal controls does not promote growth.(3) A recent study evaluated the lung microbiome composition in patients with early rheumatoid arthritis (60% with abnormalities on chest CT), sarcoidosis, and healthy controls.(28) Similar to observations in IPF patients,(7) diseased patients had reduced bacterial species diversity compared to controls, with selective absence of *Paraprevotellaceae*, *Chryseobacterium*, and *Burkholderia* spp. in diseased lungs.(28) Further, community structure differed between patients and controls, but was similar in rheumatoid arthritis compared to sarcoidosis cohorts, despite significant differences in age and smoking history. This observation led the authors to hypothesize a role of airway mucosal inflammation in shaping the lung microbiome structure in autoimmune/inflammatory diseases.(28) However, these results are somewhat contradictory to previous findings that community diversity and structure was not different when comparing mixed ILD, sarcoidosis, and healthy controls.(29)

From lung microbiome alterations to treatment strategies in ILD

The majority of our knowledge to date regarding the impact of the lung microbiome in fibrotic lung disease relates specifically to IPF and can be summarized as follows: (1) increased bacterial burden and over-representation of potential pathogens are associated with disease exacerbations and progression;(5–7) (2) there appears to be a specific host immune response to an altered lung microbiome and associated with prognosis;(24, 25, 27) and (3) there is clear harm in administration of immunosuppressive drugs to patients with IPF,(18) possibly due to propagation of detrimental microbiome alterations. Therapy directed at the microbes themselves could include antibiotics to reduce bacterial burden or target specifically identified organisms, vaccination to reduce the risk of infection with specific

pathogens, or interventions aimed at reducing immigration of bacteria to the lungs (i.e. reducing aspiration from the oropharynx).

Prior to clear knowledge of specific microbiome alterations in ILD, Shulgina and colleagues(9) conducted a randomized, placebo-controlled trial assessing the impact of co-trimoxazole on 12-month FVC change in patients with idiopathic interstitial pneumonia (over 90% of the cohort had IPF). This study was unable to demonstrate that co-trimoxazole reduces disease progression (as measured by change in forced vital capacity in 12-months, the primary endpoint) or death. With a high rate of dropout due to treatment intolerance, a per-protocol analysis was conducted and indicates a possible benefit in treatment-adherent subjects.(9) Retrospective data also suggests that IPF patients receiving invasive ventilation and corticosteroids who also receive co-trimoxazole or a macrolide antibiotic have a better prognosis compared to not receiving these agents.(30) Interpretation of per-protocol and retrospective analyses must be undertaken with caution due to the substantial potential for bias. The upcoming CleanUP IPF (Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis, [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02759120) identifier NCT02759120) trial aims to clarify the effect of antibiotics on disease outcomes in IPF. While human data is lacking, two separate mouse models of pulmonary fibrosis and *Streptococcus pneumoniae* infection suggest that prompt antibiotic administration following infection attenuates subsequent fibrosis exacerbation.(8) In the same report, immunization against the pneumococcal virulence factor, pneumolysin, prevents fibrosis exacerbation.(8) Additional work is needed to determine the mechanism by which specific organisms result in propagation of fibrosis, and the role of immunization and antibiotics in limiting their impact on disease progression in humans with IPF.

Another important treatment consideration is the role played by GER in shaping the lung microbiome in IPF. GER is prevalent, affecting up to 88% of IPF patients.(31) Recent data suggests that the lung microbiome is shaped in large part by silent microaspiration of bacteria from the oropharynx.(12–14) Increased bacterial burden in the oropharynx as a result of GER, with subsequent immigration into the lungs via microaspiration, is one plausible explanation for the finding of increased bacterial burden in IPF lungs compared to controls.(6, 7) Limited-quality retrospective data suggest a benefit of medical(22) and surgical (i.e. laparoscopic fundoplication)(32) treatment of GER in IPF. The benefit of medical therapy (i.e. acid suppression) is of question, however, given recent data for secondary analysis of a clinical trial showing no difference in disease progression or all-cause mortality in IPF patients treated *versus* not treated with antacid drugs.(33) The forthcoming WRAP-IPF (Weighing Risks and Benefits of Laparoscopic Anti-Reflux Surgery in Patients With Idiopathic Pulmonary Fibrosis, [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01982968) ID NCT01982968) clinical trial may shed light on the safety and efficacy of surgical management of GER in IPF. Additional study is required to determine the impact of GER, and GER-directed therapeutic interventions on the lung microbiome.

Conclusions

Advances in molecular sequencing technology in the last decade have allowed study of the role of the microbiome in health and disease. It has become clear that the lung contains a

dynamic community of microbes in health, and patients with interstitial lung disease may have systematic derangements in bacterial community composition. Evidence suggests that knowledge of lung microbiome composition in IPF may serve as a prognostic biomarker, a therapeutic target, or provide an explanation for disease pathogenesis.

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KEY POINTS

- Advances in molecular sequencing technology in the last decade have allowed study of the role of the microbiome in health and disease.
- The lung contains a dynamic community of microbes in health, and patients with interstitial lung disease may have systematic derangements in bacterial community composition.
- Existing evidence suggests that knowledge of lung microbiome composition in IPF may serve as a prognostic biomarker, a therapeutic target, or provide an explanation for disease pathogenesis.

Figure 1.

Evidence for an association of lung microbiome alterations with disease progression in IPF. In **Panel 1A**, Molyneaux and colleagues(7) demonstrated that IPF patients had significantly higher bacterial burden compared to COPD and healthy controls. In **Panel 1B**, the same study by Molyneaux and colleagues(7) demonstrated that among IPF patients, higher bacterial burden in the lungs is associated significantly shortened progression-free survival. In **Panel 1C**, Han and colleagues(5) demonstrate in a separate IPF cohort that having a specific *Streptococcus* or *Staphylococcus* OTU present with relative abundance above a specified threshold is associated with a clinically significant reduction in progression-free survival time. Shown here is a Kaplan-Meier plot with patients stratified by threshold of 3.9% relative abundance of *Streptococcus* OTU 1345. ***Plots reproduced with permission***.

Figure 2.

Summary of hypotheses and evidence for the role of bacteria in IPF pathogenesis. Shown is a graphical representation of evidence for a role of the lung microbiome in IPF pathogenesis. Given existing evidence, it is plausible that lung bacteria may represent the source of repetitive epithelial injury, activation of host innate immune system response, and drive progressive lung scar formation. These microbiome aberrations may arise from (1) abnormal gain of bacterial burden via increased microaspiration due to GERD, highly prevalent in IPF patients; and/or (2) slowed removal of bacteria from the lungs due to impaired mucocilliary clearance. Host innate immune activation appears to be driven by bacteria, and may result in progressive lung scarring.