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Airway Microbiome in Respiratory Diseases

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ABSTRACT

The airway microbiome is a dynamic and diverse ecosystem of bacteria, viruses, and fungi that contributes critically to respiratory health and disease. In health, microbial communities maintain homeostasis through interactions with epithelial barriers and host immune responses. Dysbiosis, or imbalance of these microbial populations, is increasingly recognized as a central factor in the pathogenesis of respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and pneumonia. Shifts in microbial diversity, enrichment of pathobionts, and disruption of host–microbiome interactions contribute to inflammation, impaired immunity, and disease progression. Advances in sequencing and bioinformatics have enabled detailed characterization of airway microbiota, while environmental exposures, host genetics, and lifestyle factors have been identified as key determinants of microbial composition. Emerging evidence highlights the therapeutic potential of microbiome modulation through probiotics, prebiotics, antibiotic stewardship, and personalized medicine approaches. Future directions include longitudinal studies, integration of multi-omics, and well-designed clinical trials to better define causality and therapeutic opportunities. Understanding the airway microbiome offers significant promise for novel prognostic markers and targeted interventions in respiratory disease.

Keywords: Airway microbiome**,** Dysbiosis**,** Respiratory diseases**,** Probiotics and prebiotics, and personalized medicine.

INTRODUCTION

The respiratory microbiome varies systematically along the length of the respiratory tract, with the highest diversity observed in the upper airway and a progressive decrease towards the lower respiratory tract. The healthy upper airway microbiome is dominated by Streptococci, Neisseria, Prevotella, Rothia, and Haemophilus. The virome is complex and characterised by phages and herpesviruses. The mycobiome largely comprises Candida and Saccharomycetales. Sputum samples represent a mixture of material derived from the upper and lower respiratory tracts. Consequently, sputum is an imperfect surrogate for the lower airway microbiome, especially in cystic fibrosis patients, where sputum volumes are high. Bacterial concentration is an order of magnitude lower in the lower respiratory tract compared to the upper airways. The biodiversity in healthy lower respiratory tract samples is dominated by Bacteroidetes, Proteobacteria, and Firmicutes, with Streptococcus, Prevotella, and Veillonella among the most abundant genera. The lower respiratory tract virome is dominated by Anelloviridae, herpes viruses, and human papillomavirus, while the mycobiome commonly includes Ceriporia lacerata, Saccharomyces cerevisiae, and Penicillium brevicompactum. The healthy respiratory microbiome is transient and is maintained by inhalation of ambient environment microbes, micro-aspiration, and mucosal dispersion. The removal of microorganisms occurs via mucociliary clearance and immune defences [1]. The analysis of airway microbiota is a relatively recent development. The identification of microorganisms that correlate with specific conditions has been largely completed. The number of clinical correlations linking airway microbiota with disease progression and outcomes is increasing rapidly, providing important prognostic insights. An improved understanding of the mechanisms underpinning these associations has the potential to reveal new therapeutic targets. It is therefore

essential that this research is directed by important clinical questions so that the outcomes ultimately benefit patients [2].

The Role of Microbiome in Respiratory Health

The airway microbiome comprises the microbial communities residing in the respiratory tract, with a complex flora of bacteria, viruses, and fungi that plays an essential role in maintaining respiratory health. The airway microbiome communities contribute to the maintenance of respiratory homeostasis [3], underscoring the importance of this ecosystem [4].

Dysbiosis and Its Impact on Respiratory Diseases

Dysbiosis is an imbalance or alteration of the microbial communities in the airways that deviates from those found in healthy individuals [5]. This altered microbiome can lead to the loss of beneficial effects exerted by commensal microbes. For example, dysbiosis may disturb the protective function of the microbiota by affecting the bacterial species that contribute to epithelial integrity and host immunoregulation [5]. A reduction of these commensal bacteria can result in the proliferation of pathogenic species such as Haemophilus, Moraxella, and Pseudomonas, which can induce hyper-immune responses and disrupt epithelial surfaces. Excessive bacterial growth can trigger proinflammatory signaling cascades through the release of various chemokines, cytokines, and other mediators, activating multiple inflammatory pathways. Supporting evidence shows that respiratory diseases are frequently characterized by microbiome dysbiosis that influences the onset and severity of symptoms [5]. The pathological impact of altered airway microbiome composition is considered a central element in the progression of many respiratory infections [1].

Definition of Dysbiosis

Dysbiosis is an alteration of the members of resident microbial populations, which has been frequently reported in airway diseases, and the existence of a dysbiotic microbiome increases the likelihood of respiratory disease [1]. Emerging evidence suggests that changes in the airway microbiome are associated with the pathogenesis and progression of several common respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and pneumonia [3]. Specific respiratory pathologies may be associated with increased abundance of pathobionts or with shifts in the global composition of resident microbiomes [3].

Mechanisms of Dysbiosis in Respiratory Conditions

Dysbiosis, a disruption of the microbial ecosystem, constitutes a pivotal mechanism linking altered airway microbiomes to respiratory diseases. Under homeostasis, the human respiratory tract experiences a balance among microbial immigration, elimination, and reproduction of residents that sustains a distinctive community characterized by taxa such as Prevotella, Streptococcus, Veronococcus, Fusobacterium, and Haemophilus [6, 3]. When pathology ensues, the lung environment is transformed, an alteration that rapidly shapes regional growth conditions and yields disease-specific microbial communities. Concomitant changes in the upper and lower airways may occur, but pathogens enriched in the lung are often undetected at the oropharynx, underscoring the importance of direct sampling for accurate characterization. Chronically diseased lungs, investigated either longitudinally or cross-sectionally, most commonly reveal reduced microbial diversity or dominance by one or two taxa [6, 3].

Common Respiratory Diseases Associated with Microbiome Changes

Microbiome dysbiosis underlies several common respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and pneumonia [1]. In these conditions, an airway microbiome less diverse than, and compositionally distinct from, that of healthy individuals is generally observed, although it remains unclear whether these microbiome changes are a cause or a consequence of disease [1]. In patients with asthma, airway microbial diversity tends to be lower than in healthy controls, with an increased abundance of Moraxella and Neisseria and decreased Streptococcus. Among adult asthmatics, sputum bacterial load increases and alpha-diversity decreases with disease severity, and patients with corticosteroid-resistant asthma harbor more Haemophilus parainfluenzae in their airway microbiome than corticosteroid-sensitive patients. COPD is likewise characterized by decreased bacterial community diversity of the airway microbiome relative to healthy individuals; an increased abundance of Streptococcus, Neisseria, and Pseudomonas is observed during acute exacerbations of COPD compared to stable disease [1, 4, 5].

Asthma

Asthma is characterized as chronic airway inflammation. Recent studies have linked specific changes in microbiome structure with asthma, implicating these alterations in the development and progression of the disease [7]. The bronchial tree harbors a characteristic yet disturbed microbiota in asthmatic individuals. As research continues to identify microorganisms that impact airway homeostasis, it becomes increasingly apparent that

microbiome dysbiosis plays a central role in the propagation of respiratory diseases 8. Alternative interpretations remain under exploration. For example, a microbiota enriched with Proteobacteria could damage the bronchial epithelium and promote inflammation. Variations in microbial composition are observed between inflammatory phenotypes; microbial correlation networks differ significantly between eosinophilic and non-eosinophilic asthma, underscoring the microbiome's potential influence on disease phenotype [9].

Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airway obstruction that leads to a progressive decline in lung function. COPD is predominantly caused by inhalation of tobacco smoke, but host factors such as genetics can also contribute to individual susceptibility [10]. Historically, colonization of the lung by bacteria was believed to be a feature exclusive to COPD exacerbations. However, culture-independent studies have shown that the closed environment of the lungs is inhabited by a distinct microbial community. The sputum microbiome is distinct between COPD and health, independent of smoking history [10]. This microbial community is characterized by a higher bacterial load and reduced species diversity compared to the healthy lung. The bacteria Haemophilus, Moraxella, and Streptococcus have all been identified as core taxa within the COPD microbiome. The presence of these organisms can drive persistent inflammation and secondary injury to the surrounding airway epithelium. Interaction between the microbiome and host epithelium also reduces macrophage functionality, creating a host environment that is more vulnerable to secondary infections [10].

Cystic Fibrosis

Cystic fibrosis (CF) is a life-limiting autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that lead to CFTR protein malfunction and affect multiple organs, especially the lungs [11]. This genetic defect impairs mucociliary clearance and antimicrobial defenses and creates a niche for microbial colonization. Chronic infections by bacteria, viruses, and fungi trigger airway inflammation and lung damage that begin early in life. Although mono-specific infections such as Haemophilus influenzae or Staphylococcus aureus during early life and Pseudomonas aeruginosa or Burkholderia cepacia complex in adult CF continue to have high clinical importance, molecular approaches have revealed a complex microbiome comprising various pathogens and anaerobic bacteria [11]. Thus, the notion of sterile lower airways has shifted to an understanding of diverse microbial communities governed by the gut microbiome whose disturbances may initiate CF-related chronic infections [11]. Analysis of the lung microbiome of CF patients already disturbed in early life established associations between antibiotic treatment, inflammation, and microbiota composition [12]. For example, microbial community changes correlate with severe declines in lung function. The excessive inflammatory responses observed in murine bronchopulmonary infections by P. aeruginosa underscore the link between the microbiome and disease severity. Since thick mucus in CF patients supports microbial growth and is associated with recurrent pneumonia and bronchitis, these microbiome characteristics influence the rate of lung destruction and respiratory failure [13]. The upper and lower airway microbiomes thus represent potential therapeutic targets in CF. Alterations in the airway microbiome also contribute to the pathogenesis of asthma, chronic obstructive pulmonary disease (COPD), and pneumonia. For example, severe asthma cases harbor an exceptionally rich and diverse microbiome heavily enriched with Proteobacteria. During COPD exacerbations, pathogens including Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae replace the microbial community's resident dominant bacteria. In pneumonia, pathogens such as S. pneumoniae and Staphylococcus aureus, although present in a healthy lung microbiome, become more abundant and less susceptible to immune clearance [13]. In common, these diseases exhibit airway microbiome dysbiosis, a shift in relative and absolute microbial abundances away from a healthy reference state that compromises respiratory defenses and facilitates pathogen colonization. Airway microbiome disturbance, whether radically precipitated by a case of dysphagia or as a chronic form of dysbiosis, contributes to the development and progression of numerous respiratory diseases, emphasizing the microbiome's central role in respiratory health maintenance [13].

Pneumonia

Pneumonia is an inflammatory condition of the lung parenchyma with high incidence and mortality worldwide [1]. The airway microbiota can protect the host against pneumonia [14]. Studies have found that lung microbiota and host immunity are important factors for homeostasis of the respiratory system. In studying the airway microbiota of patients with lower respiratory tract infections (LRTIs), no significant difference in microbial diversity was observed between those with and without pneumonia. Other work has found that the upper and lower airways have different dominant bacterial communities [14].

Methods for Studying the Airway Microbiome

Sampling of the airway microbiome is achieved via mouth rinsing, collection of saliva, or oropharyngeal swabs to circumvent specimen collection by expectoration or throat swabbing [2]. Sputum induction is a non-invasive method to collect airway secretions for evaluating airway inflammation and harvesting airway-microbiome content. Bronchoscopy allows for direct collection of samples in the lower airway through bronchial brushings, bronchoalveolar lavage (BAL), and biopsies, each providing unique insights into lung microbiology. Sequencing of these specimens relies on targeted approaches focusing on specific marker genes or whole-genome shotgun sequencing to profile the entire metagenome. Microbial genome assembly and binning enable recovery of metagenome-assembled genomes (MAGs), with new annotation tools facilitating the identification of unknown genes and ecological trait prediction. Experimental design incorporates the temporal dimension, crucial for investigating microbial community metabolism and dynamics, as well as perturbations like infection or antibiotic treatment [2]. The management and analysis of data employ a plethora of tools and pipelines tailored to different research aims. High-throughput community sequencing analysis utilizes applications such as QIIME and mothur. Multivariate space methods assist in deciphering community ecology, complemented by reproducibility-focused software like phyloseq. Diversity estimation employs nonparametric techniques and sample coverage models, supplemented by laboratory and field methods for ecological evaluation. Statistical tests, including those based on Shannon diversity, support community comparison, while broader analyses encompass microbial variation and geographic distribution in human microbiomes [15]. Fundamental concepts of community resistance and resilience inform experimental design, with MALDI-TOF MS serving to differentiate bacterial species. Specific analyses examine microbiota responses to viral infections and treatment effects mediated by antibiotics or corticosteroids, elucidating how airway microbiotas are modulated in respiratory conditions [2, 15].

Sampling Techniques

The airway microbiome is rapidly gaining attention from numerous perspectives, including epidemiology, clinical medicine, and microbial ecology. A precise and accurate description of the airway microbiome and its components is essential [16]. To this end, methods of sampling the lower airway microbiome must be systematically evaluated. Direct comparisons of oral, nasal, and protected and unprotected lower airway samples obtained by bronchoscopy from two different lung lobes in a large population are used to address this challenge. This methodological investigation clarifies the characteristics of the upper and lower airway microbiome and guides best practices when studying airway microbiota by bronchoscopy [16].

Sequencing Technologies

Sequencing Technology, a number of factors must be taken into account when studying microbiomes associated with the airways; these include the choice of sample type and location, as well as the selected sequencing technology and data analysis approach [1]. Diverse sampling methods are utilized to obtain microbiome data from the airways and lungs. While sputum and oral wash samples are simple to collect, their usefulness is limited due to contamination from other parts of the body. Protected specimen brushes provide samples that are localized to a small area but represent only the epithelial surface and are therefore an incomplete estimate of the total bacterial population [15]. Bronchoalveolar lavage (BAL) samples can be obtained from defined locations in the lungs and are widely used; however, assessing spatial relationships is difficult because microbes can move freely between various regions. To study the microbial composition and structure of ecosystem niches effectively, tissue samples are preferable because they reflect microbiota attached to the epithelial surface, but collecting sterile lung tissue is invasive [15].

Bioinformatics Approaches

Knowledge of the airway microbiome has the potential to enable novel symptomatic and curative therapies, of particular relevance in the face of the persistent threat from infectious and chronic respiratory disease. Bioinformatics approaches, such as QIIME, mothur, and phyloseq, enable microbiome datasets to be analysed, comprising microbial diversity estimation, taxonomic classification, descriptive community analyses, and multivariate statistical tests [2]. Microbiota composition and functional profiles can be predicted, and these data integrated with microarray and metabolomic data [17]. Studies using these systems profiled airway microbiota during the development of asthma and cystic fibrosis. Longitudinal sampling demonstrated that acquisition of antibiotics such as azithromycin is associated with a reduction in serum inflammatory markers and a decrease in Pseudomonas abundance. Adaptive symbiotic relationships in host-associated microbial communities promote resistance and resilience of exposed communities to perturbation. Methods such as Dirichlet multinomial mixtures (DMMB) characterise bacterial communities in a single, internally consistent statistical framework [17]. Analysis

of public 16S rRNA gene datasets from asthma, COPD, and ILD studies identified community clusters that are associated with disease and that may be further utilised for predictive analyses [17].

Factors Influencing Airway Microbiome Composition

The composition of the airway microbiome is shaped by a complex interplay of environmental factors, host genetics, and lifestyle choices [18]. Exposure to airborne chemicals, contaminants such as tobacco smoke, and aeroallergens alters microbiome profiles, increasing or diminishing the abundance of specific microbes [19]. Slower mucociliary clearance, epithelial damage, inflammation, and associated dysregulation of immune responses often cause these alterations, although the precise mechanisms remain elusive. Despite this complexity, variations in airway microbial communities are consistently linked to heightened susceptibility to respiratory diseases and other adverse health outcomes [20].

Environmental Factors

Environmental factors exert potent effects on the airway microbiome, impacting both acquisition and growth of respiratory tract bacteria and, consequently, overall ecosystem dynamics [7]. The healthy lung has long been considered sterile, with only recent analysis by sequencing technologies demonstrating a diverse microbial community present along the respiratory tract. Some appear to be constitutive members, adapted to the host environment and contributing, potentially, all the necessary residence elements of the island ecosystem (specific growth rate, immunity, efficiency of elimination), while others are probably transient, derived from external deposition and requiring spatial representation to become permanent [7]. By contrast, major disruption of the lung microbiome in respiratory disease is accompanied by dramatic shifts in community composition and dispersion, greatly increased bacterial burden, and the emergence of dominant pathogens. These observations underscore the remarkable sensitivity of the lung environment to disease-induced modification and suggest that the airway microbiome is intrinsically linked to lung homeostasis [21]. Interactions between members of the human microbiome and the immune system are of direct relevance to the pathophysiology of airway diseases. Altering the microbiome in mice using perinatal antibiotics resulted in exaggerated responses to aeroallergens in adult animals that were reversed by subsequent recolonisation with a healthy gut microbiome. Antibiotic treatment of adult mice elicited no such result, while alterations in gut microbiome composition potentiated the inflammatory stimulus. These data suggest that early-life microbial encounters contribute causative immunoregulatory signals and that at least a component of this education proceeds via gut-lung crosstalk [18].

Host Genetics

Microbial communities that develop early in life rapidly diverge between subjects, giving rise to inter-individual variation in composition [22]. The same host gene can affect the relative abundance of multiple bacteria; these bacteria often occupy very similar ecological niches, as indicated by their strong correlation in abundance. Host genetic variation associated with the airway microbiome is found primarily among genes involved in mucosal immunity, pinpointing likely mediators of host-microbe interactions at the airway mucosa and indicating specific targets for further functional analysis [22]. Heritability analyses estimate that host genetic variation contributes to explaining roughly one-tenth of the variation in bacterial abundance among humans [22]. Diverse populations of microorganisms inhabit nearly every surface of the human body, forming the human microbiome. Under healthy conditions, the relationship between microbes and the host is symbiotic, providing physiological benefits. Imbalances in bacterial communities can lead to dysbiosis, linked to diseases like sinusitis, COPD, and asthma [22]. The microbiome is a complex phenotype influenced by environmental and genetic factors. Understanding how host genetics shape the microbiome and how the microbiome modulates immunity is fundamental to characterizing many mucosal diseases. The airway microbiome develops early in life and is shaped by factors such as mode of delivery, breastfeeding, antibiotic use, tobacco smoke, and pathogens [25]. Recent data suggest that host genetics significantly influence microbiome composition, with heritability estimates indicating genetic contribution to the abundance of certain bacteria. Studies using twin pairs show more similar microbiomes among related individuals, supporting a genetic effect. Quantitative trait locus approaches have identified host gene variants influencing specific bacterial abundances. However, environmental effects complicate these studies; for example, some research failed to find host genotype effects on the gut microbiome. To overcome environmental confounding, studies focused on the Hutterite population, which minimizes environmental variation through a communal lifestyle [22]. This population, descended from 64 founders, allows more accurate analysis of genetic influences. Previous research on the Hutterite gut microbiome demonstrated genetic effects, leading to current investigations of the upper airway microbiome, specifically the nasal vestibule and nasopharynx. Findings show that host genotype influences the airway microbiome, with immune pathway gene expression playing a key role [22].

Lifestyle Factors

Several lifestyle factors shape the ecological balance and composition of the airway microbiome, thereby poisoning the relationship between airway microbes and the respiratory system. Air pollution, smoking, diet, and other lifestyle components influence the airway microbiome [23]. Air pollution aggravates asthma, COPD, and other diseases. The airway microbiome changes in response to air pollution. Large construction projects, along with the consequent increases in dust particles, lead to changes in the airway bacterial composition in adults. Higher concentrations of particulate matter cause persistence of antimicrobial resistance genes, resulting in alterations in the airway microbiome. Smoke exposure has a major impact on the airway microbiome [23]. The airway microbiome of smokers differs from that of nonsmokers and former smokers. Cigarette smoking leads to changes in the oral and oropharynx microbiomes and is associated with Candida in the upper respiratory tract. A direct causal association exists between smoking and changes in the lung microbiomes in mice. Dysbiosis in the airway microbiome resulting from smoking is mediated by inflammation and impaired immunity. Malnutrition also affects the airway microbiome, and nutritional status is associated with some respiratory diseases. The diverse composition of microbiome communities in the upper respiratory tract is strongly associated with BMI values. The nasal and oral airway microbiomes show clear correlations with BMI. Stunting in children causes an imbalance in the lung microbiomes that triggers an increase in respiratory infections. Microbial composition in the sputum of healthy individuals differs with dietary preferences. Sleep duration is another lifestyle influence on the airway microbiome [23]. It affects the microbiome diversity in the oral cavity and pharynx. Host genetics, environment, geography, and lifestyle are tightly intertwined and have a collective impact on the airway microbiome [23].

Therapeutic Implications of the Airway Microbiome

The therapeutic implications of the airway microbiome have been extensively investigated. Probiotics, prebiotics, and antibiotic stewardship have therefore been proposed to influence the composition of the airway microbiome [1]. Although these studies suggest that the early-life airway microbiome could be a target for therapeutic intervention, a deeper understanding of the dynamics of airway microbial communities is essential before therapeutics based on the airway microbiome can enter clinical practice [2].

Probiotics and Prebiotics

Research into the administration of probiotics and other microbiota modulators has begun to elucidate their potential in the prevention and treatment of lung diseases. Probiotics, defined as live microorganisms that, when ingested in adequate amounts, confer a health benefit on the host, have been thoroughly studied and account for the majority of products administered to patients [6]. Prebiotics, or substrates that are selectively utilized by host microorganisms to generate a health benefit, represent the second largest category of such treatments. Additional intervention categories include synbiotics, (co-)polysaccharides, fermented foods, functional foods, postbiotics, and pharmaceuticals [6]. These microbiota-targeting products can exert bactericidal or bacteriostatic effects, promote competition for nutrients, or modulate the local environment to influence microbial populations. Probiotic bacteria further contribute by producing molecules that directly inhibit pathogens, facilitating biofilm formation through quorum sensing and signaling, or enhancing mucosal barrier integrity to reduce invasion [6].

Antibiotic Stewardship

The airway microbiome is a determinant of respiratory health and disease. Airway resident microbial communities contribute to keeping the respiratory tree in a healthy physiological state. Disruptions to this homeostatic state of the airway microbiome result in a disease-associated defective microbiome and promote a variety of respiratory pathologies, bronchial asthma, chronic obstructive pulmonary disease, cystic fibrosis, lung cancer, and pneumonia. Microbial communities are exposed to several factors that can temporally and spatially constrain the colonization at each airway niche [21]. The microbial community is spatially influenced by the anatomical proximity and the cross–talk between the oral cavity and the respiratory tract. The air filtration process, the nutrients availability, and the immune defences are also relevant local factors for bacterial growth and colonization along the respiratory tree. Several environmental or host factors, such as atmospheric pollution, cigarette smoke, transient infections of the upper respiratory tract, immune status, age, and lifestyle, have a clear impact on the airway microbiota, as well. Furthermore, the risk of developing respiratory diseases is often linked to a combination of environmental, exposome, and host factors, and it likely involves specific airway microbial imbalances. Airway microbiota has an important influence on the effectiveness of therapies, antibiotic resistance, and antimicrobial tolerance, as well [21, 24]. Modulation of the airway microbiota is an emerging part of current therapeutic strategies in chronic respiratory diseases and can be achieved by several approaches, such as probiotics, prebiotics, antibiotic stewardship, and personalized medicine. Antibiotics are often used to prevent or treat pulmonary bacterial

colonization or infections in respiratory diseases, frequently requiring long-term administration. Prolonged antibiotic treatment may be necessary due to the anatomical and physiological changes that occur in the respiratory tract during the progression of the disease, combined with local inflammation, as well as the persistent exposure to triggering factors, which can foster chronic infections that are difficult to eradicate [24]. In cases where the culture of a sputum specimen is unavailable, tests performed on nasal, throat, or mouth swabs can direct the choice of antibiotic treatment. Although the systemic or local use of oral corticosteroids is preferred over prolonged administration of oral or intravenous antibiotics in some respiratory conditions, sputum culturing and antibiograms are recommended during exacerbations to current and adapt therapies, particularly in patients with asthma and chronic obstructive pulmonary disease [24].

Personalized Medicine Approaches

Dysbiosis of the airway microbiome occupies a central role in the progression of respiratory disease, underscoring its importance for personalized medicine initiatives [21]. By conceptualizing the airway microbiome as a reservoir for potentially pathogenic taxa, therapeutic strategies can be tailored to exploit alternative intervention opportunities when conventional treatments lose efficacy during chronic infection. Despite the continued lack of experimental evidence clarifying the mechanisms by which specific treatments exert effects, the capacity to monitor the airway microbiome longitudinally with high resolution will facilitate the identification of key microbiota and their associated mechanisms as therapeutic targets [21].

Future Directions in Microbiome Research

The airway microbiome has emerged as a critical component of respiratory health, with dysbiosis playing a key pathogenic role in multiple respiratory diseases [1]. Despite significant advances in characterizing the respiratory microbiome, many questions remain concerning the complex interactions between microbes and the host. Future research priorities include longitudinal characterization of the microbiome through periods of health and disease, integration of multi-omics approaches to simultaneously capture information on microbial composition, function, and host response, and the development of clinical trials testing strategies to manipulate the microbiome for therapeutic benefit [1]. These efforts promise to deepen the understanding of the microbiome's contribution to disease pathophysiology and enable the translation of emerging insights into improved patient care [1].

Longitudinal Studies

Many studies demonstrated a connection between alterations of the airway microbiome and the clinical course of respiratory disease. Longitudinal studies allow examination of airway microbial community dynamics and can reveal the microbe–microbe and microbe–host interactions underlying respiratory disease progression [1]. Characterizing airway microbiome variation over time in health and disease is invaluable for understanding pathogenesis and guiding effective therapeutic development [1]. Most existing longitudinal investigations focus on chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis (CF). Intranasal influenza virus inoculation has been used to evaluate the impact of influenza on the upper respiratory tract flora. Longitudinal studies show that the core taxa of the airway microbiome are largely stable in healthy individuals, although the lower respiratory tract microbiome exhibits some temporal variation in community structure [25].

Integration with Other Omics

The airway microbiome constitutes an integrated ecosystem of microorganisms occupying the respiratory tract. Its metabolic activities influence host cells and neighboring microbes, contributing to tissue homeostasis and immune responses [2]. Under normal circumstances, this ecology is subject to strain-level and ecological-level perturbations. Functional deficits in pathogen containment mechanisms permit colonization with potentially pathogenic microorganisms (PPMs), leading to airway inflammation and inflammation-associated cycles of clinical decline [1]. Considerable progress has been made in defining host microbiome interrelationships by combining microbiome data with other high-throughput analyses (multi-omics integration), such as proteomics and transcriptomics [21]. The resultant link between community structure and host microbiome cross-talk offers significant insight into the role of the microbiome in chronic airway disease. While the clinical practitioners' perspective suggests that current knowledge remains largely descriptive, a systems biology approach integrating metagenomic with metabolomic and proteomic data has the potential to elucidate novel therapeutic targets relevant to outcome and to define critical parameters that govern clinical stability [21]. The airway microbiome and metagenome itself form an integrated part of the host–mind-microbiome interactome and thus inter-domains must ultimately be fused at a clinical level [21].

Clinical Trials

Respiratory disease continues to be a leading cause of death worldwide despite advances in therapeutics [2]. Recent therapeutic interest has centered on the human microbiome, which consists of populations of commensal, symbiotic, and pathogenic microorganisms with mutually beneficial relationships with various human tissues, including the airways. While the influence of the gastrointestinal microbiota on human health and disease is well established, the contribution of the airway microbiome remains poorly understood [2]. Since the development of robust birth cohorts, longitudinal studies, and mechanistic investigations are hindered by the lack of preclinical models, the first large-scale airway microbiome clinical trials have recently been published. These studies provide insight into interconnected microbiome–host mechanisms that define specific clinical phenotypes of respiratory disease [2, 21].

CONCLUSION

The airway microbiome is a key determinant of respiratory health, maintaining immune balance and epithelial integrity under normal conditions. Dysbiosis, characterized by reduced microbial diversity and dominance of pathogenic taxa, is strongly associated with asthma, COPD, cystic fibrosis, and pneumonia, where it contributes to chronic inflammation and impaired host defenses. Advances in culture-independent sequencing and bioinformatics have transformed our understanding of microbial ecology in the airways and highlighted environmental, genetic, and lifestyle influences on microbial composition. Importantly, modulation of the airway microbiome through probiotics, prebiotics, antibiotic stewardship, and personalized medicine strategies represents a promising frontier for therapy. Nevertheless, challenges remain in distinguishing cause from effect, standardizing sampling techniques, and ensuring reproducibility across studies. Future research should prioritize longitudinal and multi-omics studies, as well as clinical trials that translate mechanistic insights into therapeutic applications. By integrating microbiome science into respiratory medicine, novel diagnostic tools and targeted interventions can be developed to improve outcomes for patients with chronic and infectious airway diseases.

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