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MINIREVIEW

Microbiome-Mucosal Immunity Nexus: Driving Forces in Respiratory Disease Progression

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Abstract

The importance of the complex interplay between the microbiome and mucosal immunity, particularly within the respiratory tract, has gained significant attention due to its potential implications for the severity and progression of lung diseases. Therefore, this review summarizes the specific interactions through which the respiratory tract-specific microbiome influences mucosal immunity and ultimately impacts respiratory health. Furthermore, we discuss how the microbiome affects mucosal immunity, considering tissue-specific variations, and its capacity in respiratory diseases containing asthma, chronic obstructive pulmonary disease, and lung cancer. Additionally, we investigate the external factors which affect the relationship between respiratory microbiome and mucosal immune responses. By exploring these intricate interactions, this review provides valuable insights into the potential for microbiome-based interventions to modulate mucosal immunity and alleviate the severity of respiratory diseases.

Keywords Respiratory tract microbiome · Lung diseases · Mucosal immunity · Host-microbe interactions · Dysbiosis

Introduction

A microbiome is defined as a collection of microbes and their genetic information within a particular environment, including bacteria, archaea, viruses, fungi, and parasites (Marchesi & Ravel, 2015). In the human body, the ratio of bacterial to human cells is approximately 1.3:1, with bacteria contributing greatly to the metabolic functions of their human hosts. In particular, the colon hosts approximately 10 trillion microorganisms (Lee et al., 2021). Beyond the gut, microorganisms inhabit various other niches such as the skin, oral cavity, and vagina (The Integrative HMP [iHMP] Research Network Consortium, 2019). Moreover, contrary to previous beliefs that healthy lungs are sterile (Baughman et al., 1987; Laurenzi et al., 1961; Thorpe et al., 1987), recent findings have revealed the presence of a microbiome in the respiratory tract and it has relationship with respiratory diseases (Natalini et al., 2023; Wypych et al., 2019). Those studies, not only gut area, but also local mucosal tissue microbiome have been growth with current great next generation sequencing techniques (Dekaboruah et al., 2020; Wensel et al., 2022). Despite the growing interest in microbiome research, there is a notable bias towards studies focused on gut microbiota.

Mucosal immunity plays a crucial role in host defense, serving as both the primary defense mechanism against microorganisms and antigens, while also contributing to maintaining tolerance (Brandtzaeg, 2009). The skin, outermost part of the human body, protects the host from pathogens through keratinocyte-derived antimicrobial peptides (AMPs) and skin-resident immune cells, including innate lymphoid cells and T cells (Nakatsuji et al., 2021). Similarly, AMPs from salivary glands and epithelial cells not only protect against pathogens but also aid in wound healing and promote cell proliferation in the oral mucosa (Hans & Madaan Hans, 2014). The gastric mucosa exhibits two key characteristics of the mucosal immune system. Firstly, the presence of secretory antibodies, particularly dimeric immunoglobulin A, fortifies the epithelial barrier and prevents the colonization and penetration of microbes. Secondly, immune tolerance plays a crucial role in avoiding hypersensitivity to dietary antigens and commensal microbes, therefore maintaining homeostasis (Wu & Weiner, 2003). Despite the undeniable importance of the gut microbiome, additional efforts

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are needed to assess the roles of microbiome within other tissues, as well as their influence on mucosal immunity.

The health burdens associated with chronic respiratory diseases have become increasingly common due to factors such as tobacco use and air pollution (Labaki & Han, 2020). As reported by the Global Burden of Disease (GBD) study in 2019, the third major cause of global deaths was chronic respiratory disease (GBD 2019 Chronic Respiratory Diseases Collaborators, 2023). Chronic obstructive pulmonary disease (COPD) was the leading cause of death from chronic respiratory diseases worldwide, resulting in approximately 3 million fatalities in 2019 (GBD 2019 Chronic Respiratory Diseases Collaborators, 2023). Furthermore, the COVID-19 pandemic, traceable to the SARS-CoV-2 virus, was accountable for approximately 6 million deaths from 2020 to 2021 (COVID-19 Excess Mortality Collaborators, 2022). Lung cancer, the second most commonly diagnosed type of cancer in 2020, significantly impacts global health with 2.2 million new diagnoses and 1.8 million deaths (Ferlay et al., 2021; Sung et al., 2021). Therefore, the advanced research for overcome the various respiratory diseases is a pressing.

Despite the global impacts of respiratory diseases, very few studies have researched the relationship between respiratory diseases and the respiratory tract microbiome, with most current research focusing predominantly on the link between diseases and the gut microbiome or likely some studies with gut-lung axis. Therefore, this review sought to highlight the importance of investigating the respiratory microbiome and immune responses. The insights from this study could be crucial in understanding the intricate interactions between the microbiome, mucosal immunity, and diseases, particularly those affecting the respiratory system. This understanding is crucial for developing more effective strategies for the preventative and therapy of respiratory diseases.

Tissue-Specific Microbiome and Diseases

Although there is still debate regarding causes and effects, the association between microbiome dysbiosis and disease is widely recognized (Manos, 2022). This chapter provides a general overview of the distinct microbiomes associated with each tissue type and how these microbiomes alter in response to various diseases.

Gut Microbiome

The human body contains trillions of microbes, which are predominantly located in the gastrointestinal tract. The composition of the gut microbiota varies due to multiple factors such as age, geographic location, diet, stress, and antibiotic use (Cresci & Bawden, 2015). Numerous studies have confirmed that the gut microbiome plays a crucial role in the maturation and regulation of the immune system, the development and progression of various diseases, the production of metabolites, and the digestion process. The most abundant phyla in the gut, especially in the colon, of healthy humans are *Firmicutes*, *Bacteroidetes*, and *Actinobacteria*. At the genus level, key microbes found in the colon include *Bifidobacterium*, *Bacteroides*, *Lactobacillus*, *Streptococcus*, *Fusobacterium*, and *Clostridium*, as well as genera belonging to the *Enterobacteriaceae* family (Afzaal et al., 2022). Commensal microbes in the gut lumen interact with the immune system in the lamina propria. Segmented filamentous bacteria are key inducers of T helper 17 cell (T_h17) development. Polysaccharide A produced by *Bacteroides fragilis* interacts with regulatory T cells (T_{reg}) to balance the type 1 helper T cells (T_h1)/ type 2 helper T cell (T_h2) responses. *Clostridium* species influence T_{reg} differentiation, while *Lactobacillus* enhances the integrity of tight junctions (Uribe-Herranz et al., 2021; Zheng et al., 2020).

Continuous inflammatory state of the gastrointestinal tract is the prominent feature of inflammatory bowel disease (IBD), leading to gastrointestinal symptoms such as severe abdominal pain and diarrhea. IBD is mostly categorized into two types: Crohn's disease (CD) and ulcerative colitis (UC), both of which are closely linked to the gut microbiome. Studies have indicated an increase in *Enterobacteriaceae* and a decrease in butyrate-producing *Roseburia* and *Subdoligranulum*, as well as *Phascolarctobacterium* in both CD and UC patients (Lloyd-Price et al., 2019; Vestergaard et al., 2024). CD patients specifically have higher levels of *Fusobacterium*, *Gemella*, and *Veillonella*, along with reduced levels of *Faecalibacterium* and *Pseudomonas*, and elevated *Escherichia coli* metabolic pathways. In UC patients, *Bifidobacterium* levels are increased while *Bacteroides* levels are reduced, with enhanced metabolic pathways of *Klebsiella pneumoniae* (Khorsand et al., 2022; Vestergaard et al., 2024). Those variety of gut microbiota is closely associated to intestinal immunity. The loss of *Faecalibacterium prausnitzii* in IBD patients, which inhibits NF-κB activation and interleukin 8 (IL-8) production and promotes T_{reg} differentiation, leads to increased inflammation and a reduction in T_{reg} cells (Cao et al., 2014; Sarrabayrouse et al., 2014). Decreasing short-chain fatty acids (SCFAs)-producing bacteria, including *Roseburia* and *Faecalibacterium*, results in the failure to suppress inflammation effectively (Parada Venegas et al., 2019). The microbiota of IBD patients, particularly *Escherichia* and *Salmonella*, promote the production of inflammatory cytokines by invariant natural killer cells (iNKT) (Burrello et al., 2019). Another characteristic of IBD is an increase in T_h17. Cytokines including IL-17, IL-21, IL-22, and IL-26 secreted by T_h17 cells promote inflammation in IBD patients (Chen et al., 2022). T_h17 cells in mice

increased when the mice received gut microbiotas from IBD patients (Britton et al., 2019).

Numerous studies have investigated the gut-lung axis, demonstrating that gut microbiota significantly influence respiratory diseases. For instance, patients with respiratory tract infections exhibit decreased levels of *Ruminococcus* and *Faecalibacterium*, which are known for producing SCFAs. *Faecalibacterium prausnitzii*, in particular, is noted for its anti-inflammatory properties (Woodall et al., 2022). Respiratory tract infections can cause systemic inflammation, leading to alterations in the intestinal microbiota. This dysbiosis results in reduced SCFA production, heightened inflammation, and an abnormal immune response, potentially causing superinfection (Sencio et al., 2021). In COPD, an increase in *Streptococcus* may disrupt fatty acid metabolism, ultimately impairing lung function (Bowerman et al., 2020). In asthma, the presence of *Veillonellaceae*, which can induce T_h2 immune responses, is linked to disease severity (Wang et al., 2021). Additionally, a reduction in SCFA-producing bacteria in asthma patients can lower interferon production, impair immune cell and eosinophil regulation, and cause epithelial damage in the airways (Zhao et al., 2023).

Skin Microbiome

The human skin serves as a vital barrier against external pathogens, achieving homeostasis through the interaction between skin cells, immune cells, and skin microbes (Belkaid & Segre, 2014). The primary phyla present in healthy human skin include *Actinobacteria*, *Firmicutes*, *Proteobacteria*, and *Bacteroidetes*. At the genus level, *Corynebacteria*, *Cutibacteria*, and *Staphylococci* account for approximately 62% of the microbial sequences identified in human skin samples (Byrd et al., 2018). The skin microbiome is influenced by several factors, including topography, age, sex, and environmental elements (Skowron et al., 2021).

Psoriasis is a skin condition characterized by scaling papules and plaques. This chronic inflammatory disorder affects 2–3% of the global population and is influenced by genetic factors and imbalances in the microbe-immune system interaction resulting from skin injury, infection, and chronic inflammatory diseases (Damiani et al., 2021; Gudjonsson & Elder, 2007). Compared to healthy controls, psoriasis patients exhibit an abundance of *Cutibacterium*, *Staphylococcus*, and *Streptococcus*, and have lower bacterial diversity (Celoria et al., 2023; Fyhrquist et al., 2019).

Atopic dermatitis is a lifelong inflammatory skin disease that affects 2.6% of the global population (Tian et al., 2023). This disease is characterized by continuous itching of the skin from childhood to adulthood. Patients with this condition exhibit reduced microbial diversity and a notable increase in the abundance of *Staphylococcus aureus*, which correlates with the severity of the disease (Koh et al., 2022; Kong et al., 2012). Additionally, compared to healthy individuals, patients with atopic dermatitis exhibit an enrichment of *Streptococcus*, *Haemophilus*, and *Gemella*, and a depletion of *Dermacoccus*, *Deinococcus*, and *Methylobacterium* (Chng et al., 2016).

Moreover, skin microbiota is involved with local mucosal immunity regulating skin disease development. The increase of *Streptococcus* and *Staphylococcus* in psoriasis is correlated with T_h17 cell polarization (Liang et al., 2021). *Lactobacillus*, which is decreased in psoriasis, has the potential to treat psoriasis by reducing inflammation (Rather et al., 2018). In atopic dermatitis, a reduction in AMPs facilitates the colonization and robust adhesion of *S. aureus* to the skin. The exotoxins produced by *S. aureus* inflict direct damage on keratinocytes, precipitating inflammatory responses (Paller et al., 2019). Furthermore, *S. aureus* is positively associated with inflammatory signaling and negatively associated with skin development. Additionally, genes involved in tryptophan metabolism, immune activation, and T_h2 signaling are upregulated (Fyhrquist et al., 2019).

Female Reproductive Tract Microbiome

The microbiome of the female reproductive tract (FRT) comes to the fore in maintaining the homeostasis of the FRT microenvironment, inducing immune responses, and protecting against pathogen invasion (Amabebe & Anumba, 2018). The FRT microbiome can be broadly categorized into vaginal microbiota and upper reproductive tract microbiota (Gholiof et al., 2022). In a healthy vaginal tract, bacterial diversity is relatively low, with *Lactobacillus* species being the dominant members of the bacterial community. Four major species of *Lactobacillus* have been identified in the FRT, namely *L. iners*, *L. crispatus*, *L. gasseri*, and *L. jensenii* (Ravel et al., 2011). *Lactobacillus* produces lactic acid, contributing to a low vaginal pH that inhibits the growth of other bacteria (O'Hanlon et al., 2013). The upper reproductive tract has a more diverse but less numerous microbiota compared to the vagina (Chen et al., 2017), including bacterial genera such as *Lactobacillus*, *Gardnerella*, *Prevotella*, *Bacteroides*, and several others (Chen et al., 2017; Verstraelen et al., 2016).

Dysbiosis in the FRT, characterized by a loss of *Lactobacillus*, can lead to increased pH, colonization by pathogenic bacteria, disruption of the epithelial barrier, and inflammation (Gholiof et al., 2022). This imbalance can result in disorders such as bacterial vaginosis (BV), sexually transmitted infections, and vulvovaginal candidiasis (Chee et al., 2020). BV is the most prevalent vaginal infection, affecting 23–29% of women globally (Peebles et al., 2019). In cases of BV, there is an increase in *Gardnerella vaginalis*, *Prevotella* spp., and *Atopobium* (Ravel et al., 2013). BV-associated bacteria induce DC maturation and inflammation.

For example, *Prevotella* suppresses T_h2 responses, whereas commensal *Lactobacillus* does not affect T cell polarization (van Teijlingen et al., 2020). Additionally, BV-associated bacteria induce the secretion of pro-inflammatory cytokines IL-1β, IL-6, IL-8, IL-36γ, and tumor necrosis factor alpha (TNF-α) in vaginal epithelial cells (Gardner et al., 2020; Onderdonk et al., 2016).

Microbiome Associated with Mucosal Immunity in Respiratory Diseases

Respiratory Tract Microbiome and Immunity

In the respiratory tract, particularly in the lungs, there is a constant inward and outward movement of air, mucus, and microbes, resulting in a highly dynamic microbiome (Dickson & Huffnagle, 2015). However, the bacterial population in the respiratory tract is relatively less abundant compared to other organs. The respiratory tract is categorized into the upper respiratory tract (URT), incorporating the nasal cavity, pharynx, and larynx, and the lower respiratory tract (LRT), consisting of the airways and lungs. The URT hosts a greater variety of microbiota compared to the LRT, although some microbes are found in both areas. Nonetheless, the microbiomes of the URT and LRT are distinct (Natalini et al., 2023). At the genus level, *Corynebacterium*, *Cutibacterium*, *Moraxella*, *Staphylococcus*, and *Streptococcus* are notably abundant in nasal microbiome of URT, while *Prevotella*, *Streptococcus*, and *Veillonella* are prominent in LRT (Di Simone et al., 2023; Natalini et al., 2023).

The immune system plays a critical role in the interaction between the respiratory microbiome and host. It consists of innate and adaptive immune systems, which regulate the composition and quantity of the microbiota and are activated by microbial products in specific environments. These systems contribute to the production of antibodies and interleukins, stimulating other immune cells and preventing infections from foreign pathogens. Innate immune responses in the respiratory tract are initiated by recognizing foreign substances via receptors such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) (Invernizzi et al., 2020). Pathogenic *Proteobacteria*, known to be linked to COPD and asthma, cause severe TLR2-independent lung inflammation with neutrophil recruitment and immunopathology in mouse models (Larsen et al., 2015). NLRs, another type of host pattern recognition receptor, also contribute to host-microbiome interactions. The interaction of NOD2 with peptidoglycan from *S. aureus* and *Staphylococcus epidermidis* in the upper airway activates macrophages, increasing their phagocytic capacity (Brown et al., 2017). In germ-free (GF) mice, γδ T cells were decreased and tumor development was slower compared to specific pathogen free (SPF) mice bearing regular commensal bacteria (Jin et al., 2019a). Representative members of the lung microbiota, including *Streptococcus*, *Neisseria*, *Veillonella*, and *Haemophilus*, were significantly correlated with *T-bet* and *GATA-3* expression level, representing T_h1 and T_h2 immune responses (Nakhaee et al., 2018). Additionally, these lung commensal bacteria are capable of reducing nitrate to nitrite and nitric oxide through a process called nitrate reduction, which may contribute to mucus production and protection against various damages (Koch et al., 2017). In tuberculosis, the enrichment of *Prevotella* in lung could increase SCFAs (Segal et al., 2017). Similar to their role in the colonic lumen, SCFAs might inhibit histone deacetylases in macrophages and activate G protein-coupled receptors (GPR41 and GPR43), which then regulate the transcription of inflammatory cytokines (Liu et al., 2023). These results indicate that the interplay between the microbiome and immune cells takes a crucial role in modulating immune responses in the respiratory tract (Fig. 1).

Microbiome and Respiratory Diseases

Despite its relatively low biomass, the respiratory microbiome interacts with the respiratory immune system during the onset of disease. This chapter elucidates the intricate interplay among diseases, the microbiome, and immune cells within the respiratory system (Fig. 2).

SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the 2020–2023 pandemic, has been shown to affect the microbiome of the lung and gut, leading to systemic impacts beyond immediate respiratory symptoms.

Changes in the nasopharyngeal microbiome potentially influence the varying outcomes of immune responses and clinical symptoms seen in SARS-CoV-2 infections (Smith et al., 2021). Notably, the nasopharyngeal microbiome of severely affected patients showed significant differences compared to that of healthy individuals. Specifically, *Staphylococcus* got involved in a growth in viral load and inflammatory cytokines including IL-6 and TNF, whereas *Corynebacterium* was negatively correlated with disease severity, indicating disruption of the nasopharyngeal microbial community due to SARS-CoV-2 infection.

Numerous studies have focused on analyzing the respiratory microbiome of COVID-19 patients, revealing various changes in microbial populations in different parts of their respiratory systems. In the throat, there was an increase in *Haemophilus parainfluenzae*, *Veillonella*, *Campylobacter fetus*, *Campylobacter rectus*, *Rothia mucilaginosa*, and *Neisseria subflava* (Shi et al., 2022; Wu et al., 2021). In the

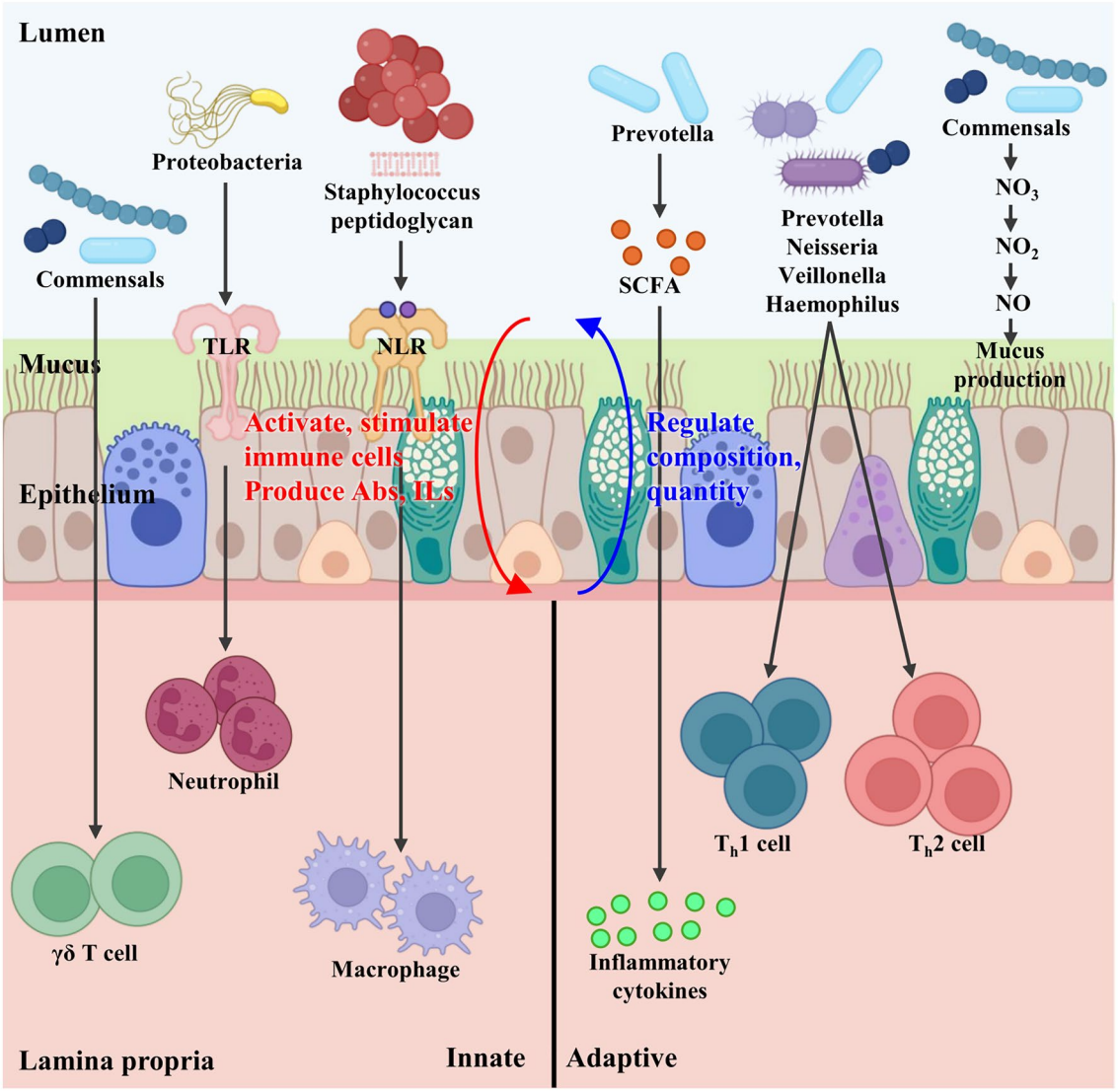

Fig. 1 Interactions between respiratory commensals and the immune system. The commensal microbiota in the respiratory tract influence a range of immune responses, both directly or indirectly. Microbes or their derived substances are detected by receptors such as TLR and NLR, which activate innate immune responses, including neutrophil recruitment, macrophage activation, γδ T cells activation, and mucus production. Additionally, the respiratory microbiota affect the adaptive immune system, influencing various types of T cells. *Abs* antibodies; *ILs* interleukins; *NLR* NOD-like receptors; *SCFA* short-chain fatty acid; *TLR* Toll-like receptors

nasopharyngeal region, there was a rise in the abundance of the *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria* phyla (Minich et al., 2021). At the genus level, *Prevotella* and *Streptococcus* were markedly abundant in COVID-19 patients (Ventero et al., 2021). *Prevotella* promote T_h17-mediated inflammation and cytokine production, resulting in cytokine storms (Larsen, 2017; Wu & Yang, 2020). In bronchoalveolar lavage fluid (BALF), increased levels of *Acinetobacter*, *Klebsiella*, *Pseudomonas*, and *Clostridium* were observed (Gaibani et al., 2021; Xie et al., 2023). Notably, *Acinetobacter*, which causes pneumonia, was found to be dominant in the lung tissues of deceased COVID-19 patients (Fan et al., 2020). Recent studies have also demonstrated that patients with SARS-CoV-2 exhibit lower microbial diversity (Zhang et al., 2021). Additionally, a significant increase in bacterial load was detected in COVID-19 patients, potentially contributing to the development of lung microbial dysbiosis, a harmful imbalance of microbial populations.

In contrast, another study examining the nasopharyngeal microbiome of patients with acute respiratory illness found no significant difference in microbiome diversity between those who tested positive and negative for COVID-19 (De Maio et al., 2020). This discordance suggests that the interplay between the microbiome and COVID-19 is intricate and thus warrants further investigation. Continued research

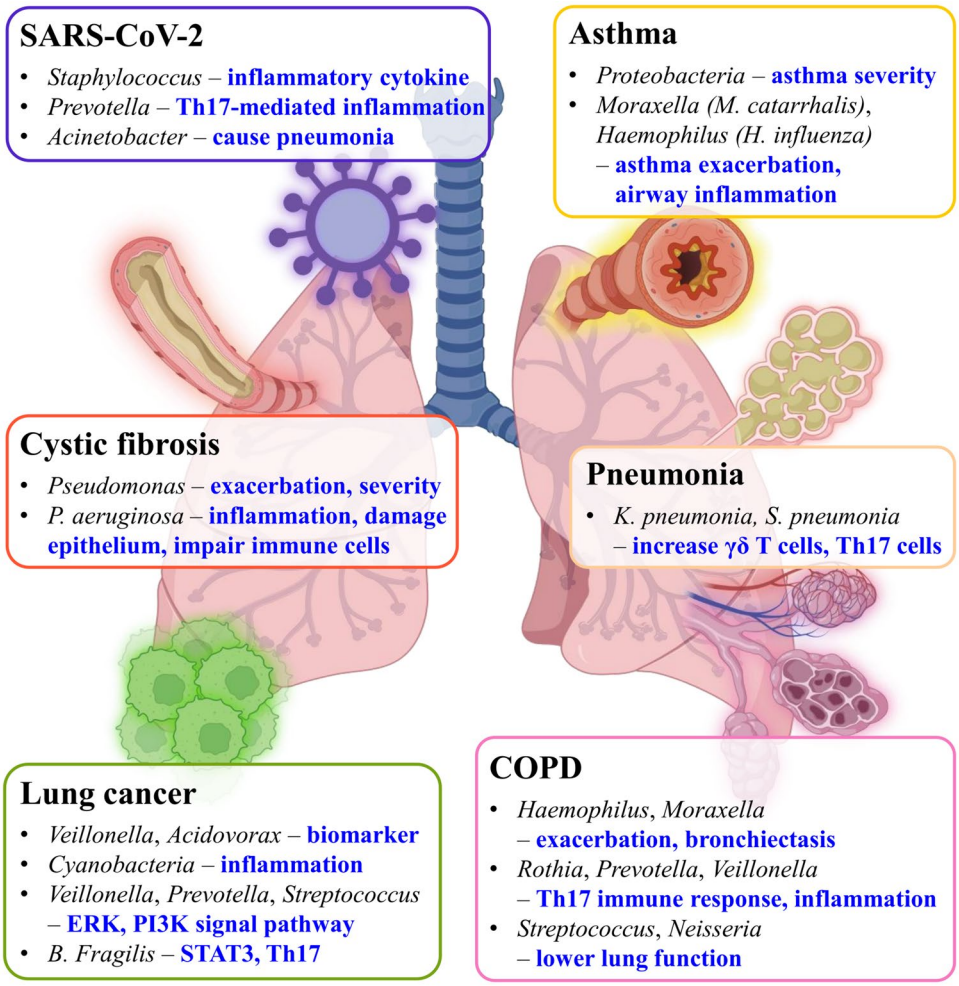

Fig. 2 Representative bacteria in the respiratory tract associated with respiratory diseases and their pathogenic immune responses. The changes in the respiratory tract microbiome associated with various respiratory diseases are briefly classified. Specific microbiomes related to immune responses are indicated. Immune responses, which are associated with microbiota, were highlighted in bold and blue letters. *COPD* chronic obstructive pulmonary disease; *ERK* extracellular signal-regulated kinases; *PI3K* phosphoinositide 3-kinases; *STAT3* signal transducer and activator of transcription 3

in this area is vital for developing a clearer understanding of how COVID-19 influences the human microbiome and its implications for patient health and treatment approaches and it might be providing the detail insight to overcome "Long COVID-19" as well.

Asthma

Asthma, characterized by airway inflammation, hyperresponsiveness, and airflow limitation, affected over 350 million people worldwide in 2019 (Song et al., 2022). The microbiome plays a decisive role in the onset and progression of asthma, with variations in microbial composition observed across different stages of the disease.

More than 90% of the bacteria in sputum samples from asthma patients belong to the *Firmicutes*, *Proteobacteria*, and *Actinobacteria* phyla. Notably, the *Proteobacteria* phylum, particularly the *Gammaproteobacteria* class, are found in higher abundance in asthma patients. Especially, *Veillonella*, *Neisseria*, *Moraxella*, *Streptococcus*, *Prevotella*, and *Haemophilus* are more prevalent in individuals with asthma (Abdel-Aziz et al., 2021; Durack et al., 2018, 2020) and these are associated with asthma severity (Abdel-Aziz et al., 2021). In nasal swab samples, *Bacteroidetes* and *Proteobacteria* levels are increased in asthma patients compared to healthy controls. At the genus level, *Haemophilus*, *Moraxella*, *Prevotella*, *Gardnerella*, and *Alkanindiges* are differentially abundant in asthma patients (Fazlollahi et al., 2018; Pérez-Losada et al., 2023). Bronchoscopy samples also indicate a higher presence of *Proteobacteria* in asthma patients, and bacteria belonging to the *Haemophilus*, *Staphylococcus*, *Neisseria*, *Fusobacterium*, and *Porphyromonas* genera are more abundant in asthma patients (Durack et al., 2017, 2018; Millares et al., 2017).

The microbiome in asthma patients varies with disease progression and is associated with mucosal immune responses. *Proteobacteria*, in particular, have the potential to impact the development and severity of asthma by inducing T_h17 or T_h2 responses (Valverde-Molina & Garcia-Marcos, 2023). A decrease in commensal microbes such as *Streptococcus* and *Gemella*, along with an increase in opportunistic microbes such as *Haemophilus*, is linked to neutrophilic

asthma. Additionally, the predominance of *Moraxella* is related to the stimulation of eosinophils in asthma (Huang et al., 2022). *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, are linked to airway inflammation including neutrophilia and eosinophilia, and increased IL-13 concentration (Azim et al., 2021; Son et al., 2020; Versi et al., 2023). *M. catarrhalis* elevates IL-33 and IL-8 levels, leading to inflammation and epithelial damage (Losol et al., 2023). Moreover, an increased presence of *Moraxella* and *Haemophilus* in the nasal passages of young children may contribute to asthma exacerbations (McCauley et al., 2022). The interaction of *H. influenzae* with macrophages activates the p38 mitogen-activated protein kinase (MAPK) pathway and increases CXCL8 production (Losol et al., 2023). The endotoxins of these bacteria influence macrophage-fibroblast interactions, leading to catabolic lung-tissue remodeling (Mouraux et al., 2018). Overall, *M. catarrhalis*, *S. pneumoniae* and *H. influenzae* are major factors in inducing asthmatic immune responses. More research and attention are required to better understand the relationship between asthma and various immune states, as current studies remain inconclusive.

Chronic Obstructive Pulmonary Disease (COPD)

COPD is demonstrated by abnormalities in the airways and alveoli and stands as a significant global health concern due to its leading role in morbidity and mortality worldwide, with the global prevalence of COPD being estimated at 10.3% (Adeloye et al., 2022).

COPD patients exhibit clear changes in the composition of their respiratory microbiome. For example, increases in *Proteobacteria* including *H. influenzae* and *Moraxella* have been reported in sputum samples (Dicker et al., 2021; Simpson et al., 2016). *Firmicutes* are enriched in patients with COPD (Tangedal et al., 2024). Additionally, *Pseudomonas*, *Streptococcus*, *Rothia*, and *Moraxella* are found in higher quantities in BALF (Einarsson et al., 2016; Ramsheh et al., 2021; Ren et al., 2018). Similar to BALF, there are increases in the relative abundance of *Streptococcus*, *Actinomyces*, *Prevotella*, *Rothia*, *Pseudomonas aeruginosa*, and *H. influenzae* in the lungs (Pragman et al., 2018; Sze et al., 2014, 2015). Moreover, there is a notable decline in microbial diversity in the COPD group (Einarsson et al., 2016; Sze et al., 2015; Wang et al., 2019).

The severity of COPD appears to be associated with tissue immune and inflammatory responses. The diversity of the respiratory tract microbiome was negatively co-related with increasing disease severity (Gupta et al., 2021). However, the dominant presence of *Proteobacteria* in sputum, particularly *Haemophilus* and *Moraxella* is positively correlated with neutrophilic inflammation, exacerbation of COPD, bronchiectasis, and an increase in mortality (Bouquet et al., 2020; Dicker et al., 2021; Mayhew et al., 2018; Wang et al., 2019). Additionally, changes in the component ratio of *H. influenza* are also central to interactions within the respiratory microbial community (Wang et al., 2016). *Streptococcus*, *Pseudomonas*, *Moraxella*, and *Rothia* in BALF are associated with COPD exacerbation (Gupta et al., 2021; Leiten et al., 2020; Ren et al., 2018). Among the bacteria, *Streptococcus*, *Rothia*, and *Moraxella* are positively related to T_h17 cell differentiation and inflammatory cytokines (Ramsheh et al., 2021; Ren et al., 2018), while *Streptococcus* and *Neisseria* are associated with lower lung function in COPD (Madapoosi et al., 2022).

Pseudomonas and *Lactobacillus* were markedly abundant in the BALF of mice with chronic lung inflammation mimicking COPD, and these bacteria exacerbated disease progression by stimulating the IL-17 A response (Yadava et al., 2016). Moreover, *Prevotella* and *Veillonella* derived from BALF of patients with chronic inflammatory airway disease are associated with increased inflammatory cytokines, lymphocytes, neutrophils, and T_h17-type responses (Segal et al., 2016). These findings suggest that respiratory-specific bacteria in chronic respiratory diseases modulate the inflammatory state of pulmonary mucosa. *Gammaproteobacteria* and *Actinobacteria* are associated with the infiltration of immune cells, including neutrophils, eosinophils, and B cells, leading to airway inflammation (Sze et al., 2015). However, additional studies are required to understand the sophisticated interactions between the inflammatory process in COPD and the respiratory microbiome, particularly their link to COPD exacerbation. Such studies could open up new avenues for promising therapeutic interventions, as well as strategies for slowing disease progression.

Cystic Fibrosis

Cystic fibrosis (CF) is known to cause the serious respiratory problems by overproduction of mucus in the lung. Recent research has highlighted a complex relationship between the respiratory tract microbiome and CF (Carmody et al., 2015; Françoise & Héry-Arnaud, 2020; Scialo et al., 2021). In CF patients experiencing disease exacerbation, the dominant microbiota in the sputum of those in a clinically stable state appears to decrease (Carmody et al., 2015). However, these patients exhibit decreased microbial diversity in their respiratory tract, coupled with an increase in the number of bacteria (Acosta et al., 2018; Feigelman et al., 2017; Sze et al., 2012). Besides, reduced diversity in the respiratory tract microbiome is associated with neutrophil inflammation and increased levels of IL-8 (Kirst et al., 2019; Linnane et al., 2021). Notably, sputum samples exhibit elevated levels of *Pseudomonas* (*P. aeruginosa*), *Haemophilus*, *Stenotrophomonas*, and *Streptococcus* (Acosta et al., 2021; Cuthbertson et al., 2020; Feigelman et al., 2017). In BALF samples,

Proteobacteria is dominant, and increases in *Staphylococcus*, *Streptococcus*, and *Pseudomonas* have also been reported (Frayman et al., 2017, 2019; Kirst et al., 2019). *Pseudomonas*, *Staphylococcus*, *and Stenotrophomonas* are predominant in the lungs of CF patients (Einarsson et al., 2021; Melnik et al., 2019). Moreover, there is a study suggesting an increase in *Pseudomonas* at the end of life in CF patients (Raghuvanshi et al., 2020). Therefore, *Pseudomonas* may also be associated with exacerbation and severity of CF.

Bacterial infections are common in CF patients due to mutations in the cystic fibrosis transmembrane conductance regulator. *S. aureus* typically infects patients in the early stages, while *P. aeruginosa* is more prevalent in the later stages (Ribeiro et al., 2023). Increasing levels of *P. aeruginosa* exacerbate lung inflammation, damage the epithelium, and activate the inflammasome in neutrophils. The constant state of inflammation makes the host more susceptible to further bacterial invasions. And macrophages function abnormally in CF, oversupplying inflammatory cytokines including TNF-α, IL-1β and IL-6, while losing their phagocytic capabilities. *P. aeruginosa* also impairs mucosal-associated invariant T cells (Bojanowski et al., 2021). Despite current knowledge, understanding the microbiome in CF patients remains insufficient to fully elucidate the underlying mechanisms. Therefore, more research is needed to gain insights into the development of disease and the microbiome to better manage disease-related complications.

Lung Cancer

Lung cancer (LC) is the most prevalent type of cancer in the world, accounting for nearly 2.1 million novel patients and 1.8 million deaths in 2018 (Bray et al., 2018). Given its substantial incidence and mortality rates, LC poses a significant global health concern. In this context, the microbiota has been increasingly perceived as a pivotal factor in cancer therapy (Roy & Trinchieri, 2017; Son & Kim, 2022). Although investigations into the capacity of the gut microbiome in cancer are actively progressing (Gori et al., 2019; Khan et al., 2012; Vivarelli et al., 2019), studies examining the lung microbiome and its association with LC are still nascent. However, recent findings are starting to shed light on this relationship. LC is primarily categorized into two groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Approximately 80% of LC cases are NSCLC, which comprises adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The residual cases are SCLC, including small cell carcinoma and combined small cell carcinoma. Much of the current research is concentrated on NSCLC (Minna et al., 2002; Thai et al., 2021).

In sputum samples obtained from LC patients, bacteria such as *Streptococcus*, *Haemophilus*, and *Granulicatella* have been found in abundance (Baranova et al., 2022; Cheng et al., 2024). Additionally, *Acidovorax* and *Veillonella* showed promise as biomarkers for squamous cell carcinoma, a subtype of NSCLC, in sputum samples (Leng et al., 2021). A decline in microbial diversity in these samples is associated with an elevated risk of LC (Hosgood et al., 2019). BALF samples obtained from LC patients exhibit significantly higher abundances of bacteria belonging to the *Firmicutes* phylum. *Veillonella*, *Megasphaera* and *Acidovorax* identified in BALF have been proposed as potential biomarkers for predicting LC (Jin et al., 2019b; Lee et al., 2016). LC patients also exhibited lower microbial diversity in their lung tissue (Liu et al., 2018; Peters et al., 2019; Yu et al., 2016). Potential opportunistic pathogens such as *Kocuria*, *Pseudomonas*, *Staphylococcus*, and *Streptococcus* have also been noted, especially in NSCLC (Apopa et al., 2018).

Microcystin, produced by *Cyanobacteria* (Tillett et al., 2000), is linked to suppressed CD36 expression in NSCLC tissue (Apopa et al., 2018). CD36 combats cancer by inducing ferroptosis and inhibiting angiogenesis in cancer cells (Jiang et al., 2024). *Cyanobacteria* also appear to be associated with the upregulation of poly (ADP-ribose) polymerase 1 (PARP1) (Apopa et al., 2018), which interacts with HuR, a protein that binds to the mRNA of pro-inflammatory cytokines such as IL-1β (Ke et al., 2019). *Veillonella*, *Prevotella*, and *Streptococcus* may bring about the upregulation of extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase (PI3K) signaling pathways through non-TLR4 receptor (Tsay et al., 2018). The ERK pathway controls genes that are crucial for the cell cycle and proliferation, whereas the PI3K pathway influences cell proliferation, cancer progression in LC (Choudhary et al., 2023). Furthermore, individuals with adenocarcinoma show a significant elevation in secondary metabolism pathways and serine-threonine protein kinase activity, with *Mycobacterium*, *Corynebacterium*, and *Negativicoccus* constituting the core microbiota (Ren et al., 2019). Experiments in animal models indicated that *Bacteroides fragilis* activates signal transducer and activator of transcription 3 (STAT3) with the support of T_h17 and induces the onset of cancer (Bou Zerdan et al., 2022). γδ T cells, stimulated by pro-inflammatory cytokines such as IL-1β and IL-23 activated by lung commensals, are associated with the development of adenocarcinoma (Jin et al., 2019a). Similar to the microbiome's influence on metastasis in other cancer types, the lung microbiome may contribute to LC by causing DNA damage, promoting tumor formation and development, and directly impairing immune system (Souza et al., 2023). These findings underscore the importance of the lung microbiome as a crucial modulator of LC pathogenesis and therapy, paving the way for further research and the development of novel diagnostic and therapeutic strategies.

Pneumonia

The risk of pneumonia is primarily associated with its role as a complication of other respiratory diseases. Consequently, studies on pneumonia and the respiratory microbiome often encompass various respiratory infections and related conditions. *Streptococcus* is predominant in BALF of pneumonia patients caused by both viruses and bacteria (Marimón et al., 2023). The specific bacteria involved in pneumonia vary depending on the mode of infection acquisition. In community-acquired pneumonia, *Streptococcus* (*S. pneumoniae*), *Prevotella*, and *Haemophilus* are abundant. In contrast, hospital-acquired pneumonia shows less bacterial impact due to the effects of antibiotic treatment (Pettigrew et al., 2021). In the case of hospital-acquired pneumonia in particular, the microbiome composition varies according to the clinical interventions. Ventilated patients show an increase in *Mycoplasma*, while intubated patients exhibit higher levels of *Pseudomonas*, *Corynebacterium*, and *Roseburia* (Li et al., 2024). In addition to the increased levels of γδ T cells and T_h17 cells, stimulated by *K. pneumoniae* and *S. pneumoniae*, can elevate cytokine production, induce inflammation, and exacerbate the pathogenesis of consecutive respiratory disease (Marrella et al., 2024). Given the complex relationships between respiratory diseases, pneumonia and the respiratory microbiome, further studies are necessary to better understand these interactions.

External Factors: Modulating the Interaction Between Microbiome and the Immune Responses in Respiratory Tract

As previously stated, respiratory tract microbiome is closely related to the host health and disease. External factors, such as lifestyle, environment, and drug, are additionally associated with the composition of microbiota (Wypych et al., 2019). Therefore, this chapter accounts for the effects of external factors including smoking, age, and particulate matter (PM) on respiratory health (Fig. 3).

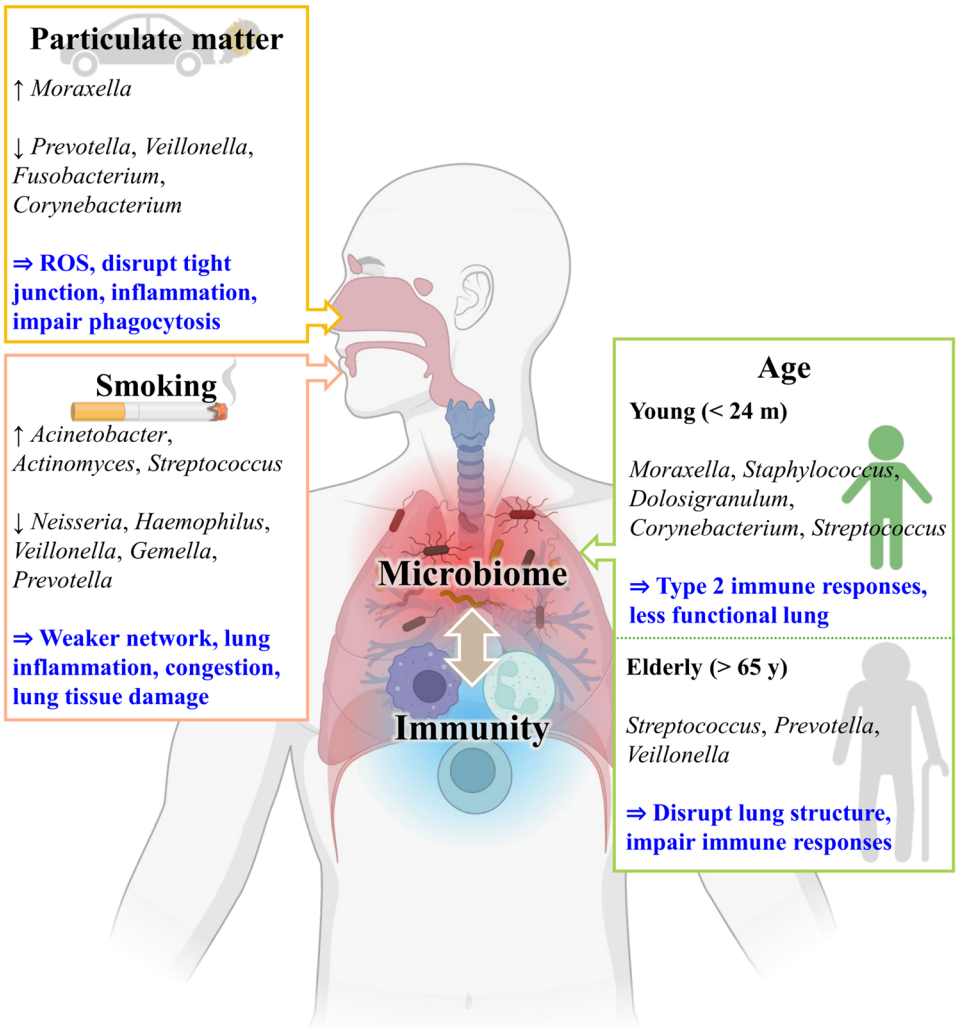

Fig. 3 External factors modulating the interaction between microbiome and immune responses. This figure illustrates the external factors that influence the interaction between the microbiome and immune responses. Changes in microbial composition and immune responses resulting from each factor are indicated. Immune responses associated with each external factor are highlighted in bold and blue letters. For the age factor, comparisons are made with adults. Specifically, the 'young' group includes individuals aged less than 24 months, and the 'elderly' group comprises those aged over 65 years old. Smoking refers to cigarette smoking, not electronic cigarettes. Particulate matter includes PM2.5 and PM10. *ROS* reactive oxygen species

First, smoking leads to dysbiosis in the respiratory tract microbiome. In smokers, microbial diversity decreases, with an increase in *Acinetobacter*, *Actinomyces*, and *Streptococcus*, and a decrease in *Neisseria*, *Haemophilus*, *Veillonella*, *Gemella*, and *Prevotella* compared to non-smokers (Campos et al., 2023; Pfeiffer et al., 2022; Turek et al., 2021). Additionally, bacteria-bacteria interactions were fewer and exhibited weaker associations in smokers compared to non-smokers (Campos et al., 2023). Besides causing dysbiosis, exposure to smoke induces lung inflammation, congestion, and structural changes in the lungs (Li et al., 2019a). These alterations contribute to chronic lung injury during pathogen infections and damage lung tissue, driving the pathogenesis and exacerbation of respiratory tract diseases (Hilty et al., 2020; Shapiro et al., 2022).

The respiratory tract microbiome changes with age, exhibiting dramatic distinct microbial compositions among children, adults, and the elderly (Kumpitsch et al., 2019). At birth, depending on vaginal delivery or C-section, *Moraxella*, *Staphylococcus*, *Streptococcus*, *Haemophilus*, *Dolosigranulum*, and *Corynebacterium* are enriched. At 1.5 months, the microbial composition is influenced by breastfeeding or formula feeding, with notable presence of *Staphylococcus*, *Moraxella*, *Streptococcus*, *Corynebacterium*, *Dolosigranulum*, and *Prevotella*. Bacterial density increases until this period, after which the diversity and density stabilize (Bosch et al., 2017; Pattaroni et al., 2018). From 6 to 24 months, *Moraxella* becomes dominant, and *Haemophilus*, *Corynebacterium*, and *Staphylococcus* also increase (de Steenhuijsen Piters et al., 2020). *Staphylococcus aureus* induces type 2 immune responses, while *Corynebacterium pseudodiphtheriticum* enhances T_h1 responses and increases the number of alveolar macrophages through the TLR3 pathway (Kanmani et al., 2017; Lan et al., 2018). In the elderly, *Streptococcus*, *Prevotella*, and *Veillonella* increase, while *Corynebacterium* and *Cutibacterium* decrease compared to adults (Kumpitsch et al., 2019; Whelan et al., 2014). Specifically, *S. epidermidis*, which stimulates epithelial cells and promotes AMP production, is found to decrease (Liu et al., 2020). Additionally, aging disrupts the lung structure, impairs function, and weakens immune responses, including those of alveolar macrophages, NK cells, and tissue-resident memory T cells (Torrelles et al., 2022). These changes increase the risk of autoimmune and infectious diseases. The less functional lungs in young age and disrupted lungs in the elderly are likely related to the instability and changes in the lung microbiome. Therefore, further studies are needed to understand these relationships better.

Air pollution is increasing, and its impact on public health, particularly from PM, is becoming more significant. Exposure to PM increases reactive oxygen species, which facilitate the entry of microbial toxins and pollutants into the bloodstream. This leads to damage of the tight junctions, weakening the response to bacterial invasion (Liu et al., 2019; Xue et al., 2020). Additionally, PM exposure activates inflammation and impairs the phagocytic ability of alveolar macrophages (Glencross et al., 2020). These changes lead to microbiome dysbiosis. At the phylum level, *Actinobacteria* and *Firmicutes* increase while *Bacteroidetes* decrease. At the genus level, *Moraxella* increases, whereas *Prevotella*, *Veillonella*, *Fusobacterium*, and *Corynebacterium* decrease with rising PM concentrations (Li et al., 2019b; Mariani et al., 2018; Qin et al., 2019). This dysbiosis in the respiratory tract leads to immune system dysregulation, ultimately contributing to the development and exacerbation of respiratory diseases (Xue et al., 2020).

Conclusion

The microbiome plays a significant role in the pathogenesis and progression of various diseases by modulating immune responses and maintaining homeostasis, thereby affecting both disease susceptibility and severity. Investigating the respiratory microbiome is crucial as a novel approach to understanding and potentially managing respiratory diseases, especially since mortality rates associated with these diseases, particularly chronic respiratory disease, are expected to increase, due to factors such as population growth and aging.

Thus, we investigated current studies to summarize the general contents of microbiota and association with local mucosal immunity in the respiratory tract. Additionally, we reported the critical fluctuation of certain microbiota in the various respiratory diseases including virus infection, asthma, COPD, cystic fibrosis, lung cancer. Last, we summarized how the external factors such as smoking, age, and particulate matter affect host health or respiratory disease progression. This review highlighted the events in the respiratory tissues unlike current most studies which demonstrating effects of microbiota from gut to other tissues. Therefore, we believe that further research into the respiratory microbiome holds promise for minimizing the side effects of current treatments and discovering new diagnostic and therapeutic options.

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Declarations

Conflict of interest The authors declare that there are no potential conflicts of interest.

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