Journal of Microbiology (2024) 62:201–216
https://doi.org/10.1007/s12275-024-00124-1

REVIEW

Application of Microbiome-Based Therapies in Chronic Respiratory Diseases

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Received: 14 December 2023 / Revised: 2 February 2024 / Accepted: 16 February 2024 / Published online: 18 April 2024

Abstract

The application of microbiome-based therapies in various areas of human disease has recently increased. In chronic respiratory disease, microbiome-based clinical applications are considered compelling options due to the limitations of current treatments. The lung microbiome is ecologically dynamic and affected by various conditions, and dysbiosis is associated with disease severity, exacerbation, and phenotype as well as with chronic respiratory disease endotype. However, it is not easy to directly modulate the lung microbiome. Additionally, studies have shown that chronic respiratory diseases can be improved by modulating gut microbiome and administrating metabolites. Although the composition, diversity, and abundance of the microbiome between the gut and lung are considerably different, modulation of the gut microbiome could improve lung dysbiosis. The gut microbiome influences that of the lung via bacterial-derived components and metabolic degradation products, including short-chain fatty acids. This phenomenon might be associated with the cross-talk between the gut microbiome and lung, called gut-lung axis. There are multiple alternatives to modulate the gut microbiome, such as prebiotics, probiotics, and postbiotics ingestion and fecal material transplantation. Several studies have shown that high-fiber diets, for example, present beneficial effects through the production of short-chain fatty acids. Additionally, genetically modified probiotics to secrete some beneficial molecules might also be utilized to treat chronic respiratory diseases. Further studies on microbial modulation to regulate immunity and potentiate conventional pharmacotherapy will improve microbiome modulation techniques, which will develop as a new therapeutic area in chronic respiratory diseases.

Keywords Asthma · Chronic obstructive pulmonary disease · Gut-lung axis · Idiopathic pulmonary fibrosis · Microbiome

Introduction

The main pharmacotherapies for chronic respiratory diseases aim to relieve symptoms, improve quality of life, and prevent exacerbation, but they still have limitations and are unable to prevent such diseases or reverse their natural course. For example, bronchodilators for chronic obstructive pulmonary disease (COPD) and antifibrotic agents for idiopathic pulmonary fibrosis (IPF), which are regarded as the mainstay for treatment, cannot hinder disease progression or resolve these diseases (Nici et al., 2020; Raghu et al., 2022). Recently, up-to-date knowledge of microbiome has been applied to treat various human illnesses, such as cancer and gastrointestinal and infectious diseases (Helmink et al., 2019; Hu & Gubatan, 2023; Juul et al., 2018; van Nood et al., 2013). In this context, the therapeutic application of microbiomes for chronic respiratory diseases is considered a suitable option to overcome the current limitations of respiratory disease treatments.

The human microbiome is a critical determinant of human health, specially, the gut microbiome (VanEvery et al., 2023). The gut microbiome is a complex and diverse community that contributes to metabolic, immunological, and protective functions (Chiu et al., 2017). Furthermore, the beneficial effects of the gut microbiome extend beyond local immunity to major body organs such as the liver, brain, and lungs (Hsu & Schnabl, 2023; Morais et al., 2021; Zhou

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et al., 2021). Therefore, an imbalance in the gut microbiome may not only impact pathological conditions in the gastrointestinal tract but also exacerbate pathologic conditions in various other organs.

Beyond the gut, mounting evidence highlights the association between an altered lung microbiome and various chronic respiratory diseases. In the past, healthy individuals were assumed to have sterile lower respiratory tracts. However, the implementation of non-culture-based metagenomic methods has made it possible to recognize microbiomes with low biomass, demonstrating the existence of the lung microbiome (Natalini et al., 2023). Based on this finding, various associations have been established between human diseases and their statuses with the lung microbiome.

The extensive research conducted on humans and other mammals has indicated that diet can substantially modify the gut microbiome (Sonnenburg & Bäckhed, 2016). This result emphasizes that microbial communities in the gut are affected by a variety of factors, such as the composition of the diet, habitual eating patterns, and abrupt dietary changes. The so-called Western diet, low in fiber and high in fat, is associated with reduced gut microbial diversity and a subsequent increase in chronic metabolic diseases, such as obesity, type 2 diabetes, and cardiovascular disease (Nogal et al., 2021). In contrast, a prudent diet, rich in dietary fiber, is widely recognized for its beneficial role (Holscher, 2017). The microbiome is a key factor to link the diet and its effects on human health.

In this review article, we provide an overview of previous publications on the lung and gut microbiomes in chronic respiratory diseases. Our focus is on the epidemiological, preclinical, and clinical evidence of potential therapeutic interventions involving the modulation of the microbiome in chronic respiratory diseases.

The Microbiome in Chronic Respiratory Diseases

Lung Microbiome

A substantial amount of research has demonstrated the potential role of the lung microbiome in chronic respiratory diseases (Natalini et al., 2023; Yi et al., 2022). Compared to the gut microbiome, the respiratory tract consists of a low-density microbiome, and location-specific niches are established throughout the respiratory tract. Therefore, repeated and standardized sampling techniques are essential to establish causality, and large-scale longitudinal studies that could minimize the effect of confounders are also required (Watson et al., 2019).

As the respiratory tract is exposed to the environment, the lung microbiome is ecologically dynamic and affected by various conditions, such as aspiration from the upper respiratory tract, clearance by the immune system, and local microbial proliferation (Ditz et al., 2020; Natalini et al., 2023). In healthy individuals, the microbiome is dominated by the phyla *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* (Yi et al., 2022). In a healthy state, microbial inflow and outflow reach a state of homeostasis. However, in pathological conditions, microbial dysbiosis occurs due to structural and microenvironmental changes, such as mucosal pH alterations, changes in local oxygen concentrations, temperature, blood flow, nutrition, and local inflammatory conditions. Dysbiosis is not only associated with disease severity, exacerbation, and phenotype but also with the endotype of the disease (Natalini et al., 2023).

The lung microbiome in patients with asthma is heterogenous, and it is linked to severity, phenotype, and other factors (Huang et al., 2015). Asthma is generally associated with increased bacterial load (Huang et al., 2011). In severe asthma, the microbiome is dominated by *Proteobacteria* and *Streptococcus* with decreased abundance of *Prevotella* and *Veillonella* (Goleva et al., 2013; Huang et al., 2011). Asthma can be classified into two phenotypes: T-helper cell (Th) 2-high and Th2-low phenotypes (Porsbjerg et al., 2023). Patients with Th2-high phenotype asthma respond well to corticosteroids and targeted biologics. The microbiome in Th2-high phenotype asthma is characterized by lower bacterial burden and diversity compared to that in Th2-low phenotype asthma (Durack et al., 2020). A higher bacterial burden with enriched *Haemophilus*, *Moraxella*, and *Neisseria* spp. is observed in Th2-low phenotype sputum and brushing samples (Durack et al., 2020). This high bacterial burden and the presence of potential pathogens may lead to increased bacterial cell wall fragments, which drive an exacerbated inflammatory response with high levels of inflammatory cytokines, including interleukin (IL)-17 (Green et al., 2014; Rahmawati et al., 2021). *Haemophilus* is known to induce IL-17-mediated neutrophilic allergic airways disease (Essilfie et al., 2011, 2012), suggesting it might be a potential therapeutic target in Th2-low phenotype asthma. This is supported by clinical studies that show that long-term azithromycin treatments can reduce the asthma exacerbation associated with decreased *Haemophilus* burden (Taylor et al., 2019, 2020; Undela et al., 2021).

Compared to healthy individuals, patients with COPD exhibit a reduced microbial alpha-diversity and increased microbial load (Sze et al., 2015). Several studies have shown that a more severe airflow limitation can be associated with lower microbial diversity (Garcia-Nuñez et al., 2014; Mayhew et al., 2018). This reduction in diversity is frequently

caused by the overgrowth of certain bacteria, primarily from the *Proteobacteria*, such as *Pseudomonas* and *Haemophilus* spp. (Galiana et al., 2014). Previous studies demonstrated that the overgrowth of these bacteria shows a statistically significant correlation with local airway inflammation, as indicated by elevated levels of myeloperoxidase, IL-8, leukotriene B4, and leukocyte elastase (Hill et al., 2000). In addition, the burden of *Bacteroidetes* and *Firmicutes* and that of *Prevotella* and *Veillonella* spp. decreased in COPD patients with overgrown populations of *Proteobacteria*. Wang et al. (2021) reported an inflammatory endotype of COPD when *Haemophilus* was predominant in the lung microbiome, as the presence of this bacterium has been associated with neutrophilic inflammation and elevated IL-1β and tumor necrosis factor (TNF) α levels. In these patients, targeted antibiotics use for *Haemophilus* might be helpful to reduce airway inflammation (Tufvesson et al., 2015). In the lung microbiome of members of the neutrophilic-balanced group, *Veillonella* and *Prevotella* are relatively abundant, and their presence is associated with elevated serum and sputum IL-17A levels (Wang et al., 2021). During exacerbation, big changes in the lung microbiome are observed in the neutrophilic-balanced group, indicating that targeted antibiotics may not be appropriate treatments for the members of this group. The differences in the characteristics of the microbiome suggest that individualized therapeutic approaches, based on individual microbiomes, could be feasible options in COPD.

The microbiome of patients with IPF is being actively investigated. The relationship between bacterial burden and disease course and prognosis of IPF has been reported in several studies (Han et al., 2014; Molyneaux et al., 2014; O'Dwyer et al., 2019). The microbiome in patients with IPF is characterized by decreased diversity and dominance of *Prevotella*, *Veillonella*, *Streptococcus*, and *Escherichia* spp. (Han et al., 2014; Molyneaux et al., 2014; Takahashi et al., 2018). Several studies evaluated the effects of antibiotics, including azithromycin, doxycycline, and trimethoprim-sulfamethoxazole, in microbiome modulation in patients with IPF, but the results were not consistent (Guler et al., 2021; Kawamura et al., 2017; Macaluso et al., 2019; Martinez et al., 2021; Shulgina et al., 2013; Varney et al., 2008; Wilson et al., 2020). Clinically, no benefit of long-term antibiotics has been reported in IPF, in contrast to those demonstrated in asthma and COPD.

In addition to that in the a forementioned diseases, the microbiome in various other chronic respiratory diseases has been investigated (Campbell et al., 2022; Chotirmall et al., 2022; Natalini et al., 2023).

Gut Microbiome

In contrast to other organs, most studies related to the microbiome in chronic respiratory disease focused on the lung microbiome instead of the gut microbiome. However, several studies reported the relationship between gut microbiome and chronic respiratory disease (Liu et al., 2023; Shi et al., 2023; Su et al., 2023).

The gut microbiome has been well studied in relation to asthma, and the maturation of the early-life gut microbiome is known to exhibit a protective effect against childhood asthma (Depner et al., 2020). Dysbiosis of the gut microbiota in early life is also known to increase the risk of developing asthma (Abrahamsson et al., 2014; van Nimwegen et al., 2011). Changes in the fecal microbiota, such as a decreased abundance of *Faecalibacterium*, *Lachnospira*, *Rothia*, and *Veillonella*, and an increased abundance of fungi, such as *Candida* and *Rhodotorula*, are also associated with asthma (Arrieta et al., 2015; Fujimura et al., 2016). Gut microbiome diversity is lower in patients with asthma than in healthy individuals (Wang et al., 2018; Zou et al., 2021). The gut microbiome is also distinguished according to endotypes, especially *Ruminococcus bromii*, *Brevundimonas vesicularis*, and *Clostridium disporicum* (Zou et al., 2021).

In patients with COPD, the gut microbiome is dominated by *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia* at the phyla level and *Lactobacillus*, *Oscillospira*, *Clostridium*, *Ruminococcus*, *Blautia*, *Treponema*, *Allobaculum*, and *Turicibacter* at the genera level (Anand & Mande, 2018; Li et al., 2021; Wang et al., 2021). However, a decrease in the abundance of *Bacteroides*, *Roseburia*, *Lachnospira*, and *Ruminococcaceae* is recorded (Bowerman et al., 2020; Lee et al., 2018). Although the results are inconsistent, dominance of specific microbiota may vary depending on the clinical features of COPD, such as stage, severity, and eosinophil count (Chiu et al., 2021; Lai et al., 2022).

Limited data exist on the relationship between the gut microbiome and pulmonary fibrosis. One such study, comprising patients with silicosis-induced fibrosis, found a relative decrease in *Firmicutes* and *Actinobacteria* abundances in the gut microbiome (Zhou et al., 2019).

Gut-Lung Axis

The role of the gut microbiome in respiratory diseases is also receiving attention and being actively studied. Though the gut and lung seem to be anatomically distinct organs, there is evidence of cross-talk between gut microbiome and the

lung, namely, the gut-lung axis (Dang & Marsland, 2019). Both the gut and lungs are developed from the embryonic foregut during development and have a common mucosal immunological system (de Santa Barbara et al., 2002; Tulic et al., 2016). During life, the upper and lower airway microbiomes are continuously affected by gastrointestinal tract migration of microorganisms by microaspiration of pharyngeal secretions or gastric juice (Yagi et al., 2022). Although microbiome composition, diversity, and abundance is considerably different between the gut and lung, changes in the gut microbiome could induce a significant dysbiosis in the lung (Cruz et al., 2021). Additionally, the gut microbiome influences that of the lung via bacterial-derived components and metabolic degradation products, including short-chain fatty acids (SCFAs) (Dang & Marsland, 2019; Enaud et al., 2020; Sharon et al., 2014). Pro- or anti-inflammatory and immunomodulatory effects of SCFAs as well as changes in SCFA levels due to gut microbiome modulation are well-reported in various studies (Eckburg et al., 2005; Kotlyarov, 2022; Ramakrishna, 2014; Reiss et al., 2016). One of the plausible pathways involves the action of SCFAs through G-protein coupled receptors (GPRs) 43 and 41, called free fatty acid receptors 2 and 3 (Kotlyarov, 2022). GPR43 is primarily expressed on immune cells, such as lymphocytes, monocytes, and neutrophils, while GPR41 is expressed in adipose tissue, pancreas, spleen, and lymph nodes (Li et al., 2018). After activation, both receptors are involved in inflammation and immunity modulation (Ashique et al., 2022). Histone deacetylase and the nuclear factor-kappa B signaling pathway are also associated with the action of SCFAs (Ashique et al., 2022).

Many studies have reported that alterations in the gut microbiome perturb host systemic homeostasis and contribute to disease development in various organs (Carabotti et al., 2015; Dash et al., 2022; Enaud et al., 2020; Rastelli et al., 2019; Thursby & Juge, 2017). In this aspect, chronic respiratory diseases are not the exception. Asthma, COPD, cystic fibrosis, lung cancer, and infectious diseases are associated with gut microbiome dysbiosis (Chunxi et al., 2020). Characterized by enrichment and diversity (Sze et al., 2012), the gut microbiome might have more effects on the local and systemic immune function than that of the lung (Hooper et al., 2012). In addition, the modulating effects and safety of the gut microbiome have been more actively investigated than those of the lung microbiome. Gut microbiome can be modulated through diet; ingestion of prebiotics, probiotics, and postbiotics; and fecal microbiota transplantation (FMT) (Quigley & Gajula, 2020). The systemic effect of gut microbiome, together with well-studied microbial modulation modalities, will inspire further studies to overcome the limitations of currently available gut microbiome modulation treatments for chronic respiratory diseases.

Therapeutic Application via Microbiome Modulation

Epidemiological Background on the Role of Fiber in Microbiome Composition

Diet significantly influences gut microbiota and its metabolites, which are directly and indirectly linked to host health (Makki et al., 2018; Sonnenburg & Sonnenburg, 2014). The impact of diet on the gut microbiome and its metabolites was elucidated by analyzing the fecal microbiome of children during their first two years of life (Tsukuda et al., 2021). In the initial phase of breastfeeding, *Enterobacteriales* predominated, together with elevated levels of succinate and decreased levels of acetate. In the later phase, *Bividobacteriales* became dominant, and higher concentrations of lactate and acetate were detected. After cessation of breastfeeding, *Clostridiales* became more prevalent, resulting in increased levels of butyrate, propionate, and acetate, similar to the typical pattern in adult feces. Among various diets, high-fiber diets (HFDs) have various beneficial effects, which are probably mediated by gut microbiota (Makki et al., 2018).

Dietary fiber includes edible carbohydrate polymers, with three or more monomeric units, that are resistant to endogenous digestive enzymes (Jones, 2014). Therefore, they are neither hydrolyzed nor absorbed in the small intestine. They belong to the following categories: (1) edible carbohydrate polymers naturally occurring in foods, such as fruits, vegetables, legumes, and cereals; (2) edible carbohydrate polymers obtained from food raw materials by physical, enzymatic, and chemical means, which have a proven physiological benefit; and (3) synthetic carbohydrate polymers with a proven physiological benefit.

A positive association between lung function and dietary fiber intake was documented in several chronic respiratory diseases (Sdona et al., 2021). The Atherosclerosis Risk in Communities study, a cross-sectional study that was conducted on men and women, showed that fiber intake from all sources, including cereal or fruit alone, had beneficial effects (Kan et al., 2008). The adjusted odds ratio (OR) of COPD for the highest versus lowest quintiles of intake was 0.72 for all fiber sources. This was the first study showing that dietary fiber was independently associated with improved lung function and reduced prevalence of COPD.

Several prospective studies have highlighted the impact of fiber on COPD. A study conducted in two separate US cohorts of women and men, including 11,580 individuals, with a follow-up period of 16 years, found that a HFD (both total and cereal only) had a correlation with lower incidence rates of COPD. Other studies carried out on a cohort of Swedish men and women yielded similar results, which imply that consuming high amounts of fiber over an

extensive period correlates with a 30–40% decreased risk of COPD (Kaluza et al., 2017; Szmidt et al., 2020). The beneficial effect was more pronounced in current smokers rather than in ex-smokers. Furthermore, a retrospective cohort study assessed the lung function of healthy individuals with normal lung function at 5-year intervals. The study revealed that a 10% decrease in dietary fiber intake below the recommended daily intake led to the development of newly acquired airflow limitations with an OR of 2.714 (Jung et al., 2021).

In asthma, the negative impact of a "Western" dietary pattern, characterized by high fat and low fiber, is widely recognized. Patients with severe persistent asthma consumed more fat and less fiber than healthy controls (Berthon et al., 2013). Conversely, increased fiber intake is significantly associated with lower asthma symptom scores (Andrianasolo et al., 2019; Saeed et al., 2020). As dietary fiber intake increased, the prevalence of asthma decreased, according to another cross-sectional study (adjusted OR for Q4: 0.656; P for trend < 0.001) (Lee et al., 2021). The key findings of each study are summarized in Table 1**.** The results from these studies indicate that the beneficial effects of dietary fiber come from the metabolism and fermentation of gut microbiota.

Preclinical Interventional Background

There are multiple methods to modulate the gut microbiome, such as the ingestion of prebiotics, probiotics, and/or postbiotics, and FMT (Mindt & DiGiandomenico, 2022) (Fig. 1). A prebiotic is defined as a substrate that is selectively utilized by host microorganisms to confer a health benefit to the host. The most widely studied and recognized prebiotic substances comprise of non-digestible dietary fibers, such as fructooligosaccharides, galactooligosaccharides (GOS), inulin, and pectin. Commensal bacteria in the colon conduct anaerobic fermentation of these complex carbohydrates, leading to the production of SCFAs.

Acetate, propionate, and butyrate are the major SCFAs; they are considered crucial mediators in regulating the immune system, displaying anti-inflammatory and immunomodulatory properties (Dang & Marsland, 2019). These molecules act locally or at peripheral sites by activating the G protein-coupled receptors (GPCRs) present on epithelial or immune cells. SCFAs affect the metabolism of T and B cells, promoting the differentiation of naïve T cells into Th1 cells, Th17 cells, and Tregs. Therefore, SCFAs influence inflammatory responses (Kim, 2021). Furthermore, SCFAs decrease the activity of group 2 innate lymphoid cells (ILC2), reducing allergic responses. Recent studies suggest that SCFAs affect hematopoietic precursors in the bone marrow, which move to the lungs, creating an anti-inflammatory environment.

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Bacteria from the *Bifidobacterium* (*e.g.*, *B. breve* and *B. longum*) and *Lactobacillus* (*e.g.*, *L. rhamnosus* GG and *L. plantarum*) genera are frequently utilized as probiotics for both preventive and therapeutic purposes.

Several preclinical studies in animal models of chronic respiratory diseases suggest that prebiotics and probiotics have therapeutic potential (Table 2). Trompette and colleagues' (Trompette et al., 2014) well-designed study showed that a fermentable pectin fiber-rich diet reduced the risk of allergic airway inflammation. Moreover, a propionate supplement yielded similar results (Trompette et al., 2014). Another prebiotic fiber, GOS, exhibited preventive effects on the development of airway hypersensitive response that were as effective as those of budesonide treatment (Verheijden et al., 2015). The efficacy of various prebiotic fibers has been debated, and there is no consensus on which is the most potent. In comparison to diets including mixtures of GOS, long-chain fructooligosaccharides, and *B. breve* M-16 V, the diets including mixtures of short- and long-chain fructooligosaccharides with *B. breve* were found to be the most effective in preventing house dust mite extract-induced airway inflammation in mice (Verheijden et al., 2016). Another study showed that *B. breve* MRx0004, a strain acquired from a healthy person's gut microbiome, was effective in a severe asthma mouse model resistant to steroid (Raftis et al., 2018). Remarkably, oral administration of MRx0004 led to decreased airway inflammation as both prophylactic and therapeutic treatments.

In a cigarette smoking exposure model, dietary fiber and probiotics have also been suggested to have a beneficial effect. *L. rhamnosus*, *B. breve*, and *B. longum* subsp. *longum* demonstrated an anti-inflammatory response in smoking-induced inflammation (Budden et al., 2022; Mortaz et al., 2015). In another study, a different method was used to modulate the gut microbiome (Jang et al., 2020). The researchers discovered that FMT from healthy controls and a HFD helped to reduce the severity of emphysema induced by cigarette smoke and decreased cell apoptosis. Moreover, the highest degree of attenuation was seen among those groups treated with both FMT and HFD. Interestingly, different fiber types, specifically non-fermentable cellulose or fermentable pectin, lead to a similar dampening of the pathological changes associated with emphysema progression and the inflammatory response. Notably, the diversity of the gut microbiome and metabolic profile, especially the SCFA profile, were distinctive (Jang et al., 2021). In an emphysema mouse model, supplementation with acetate and propionate —the representative metabolites of gut microbiota— reduced alveolar destruction and the production of proinflammatory cytokines, while supplementation

Table 1 Observational studies investigating the correlation between dietary fiber consumption and COPD and asthma

References	Study design, Contry, Cohort	n	Population	Dietary fiber measure	Outcome Assessment	Follow up	Main finding
COPD and lung function							
Kan et al. (2008)	Cross-sectional, US, ARIC	11,897	adults aged 44-66 years	66-item semiquantatitive FFQ	Spirometry, COPD based on self-reported symptoms or spirometry	N/A	High fiber diet independently associated with better lung function, reduced prevalence of COPD
Varraso et al. (2010)	Cohort, US, Nurses' Health Study, Healthy Professionals follow-up study	111,580	female nurses aged 30–55 years, men health professionals 40–75 years, no history of asthma or COPD	FFQs	self-reported COPD defined by diagnosis of COPD	16 years	A diet high in fiber, and possible specificallly cereal fiber may reduce risk of COPD evelopment
Root et al. (2014)	Cohort, US, ARIC study	12,532	adults aged on average 54 years	intervieweradministered semiquantitative FFQ	spirometry	3 years	Low fiber intake was associated with reduced measures of lung function
Hanson et al. (2016)	Cross-sectional, US, NHANES	1,921	adults aged 40–79 years (mean age 53 years)	two-interviewer administered 24 h recalls	spirometry	N/A	Low fiber intake was associated with reduced measures of lung function
Leng et al. (2017)	Cohort, US, Lovelace Smokers cohort (LSC), Veteran Smokers cohort (VSC)	2,337	adult smokers aged 40–74 years	semi-quantitative 150-item FFQ	spirometry	5.3 years	The nutrients that protect FEV1 in ever smokers could be the basis for designing personalized nutrition plans that target "optimal physiological levels" to improve lung function in ever smokers
Kaluza et al. (2017)	Cohort, Swedish	45,058	men aged 45–79 years, no history of COPD	96-item FFQ	Incident COPD cases through linkage with registry data	13.2 years	High consumption of fruits and vegetables is associated with reduced COPD incidence in both current and ex-smokers but not in never smokers
Szmidt et al. (2020)	Cohort, Swedish	35,339	women aged on average 62 years, no history of COPD	67 or 96 item FFQ	incident COPD cases through linkage with registry data	12 years	High fiber intake is a modifiable lifestyle factor which may decrease COPD risk primarily in current and ex-smokers

Table 1 (continued)

References	Study design, Contry, Cohort	n	Population	Dietary fiber measure	Outcome Assessment	Follow up	Main finding
Kim et al. (2020)	Cross-sectional, Korea, Korean NHANES	702	COPD adults aged ≥ 40 years	24 h dietary recall	COPD severity defined by spirometry	N/A	Intake of carbohydrate, protein, fiber, thiamin, riboflavin, niacin, and vitamin C was associated with decreased severity of airway impairment in elderly men with COPD
Jung et al. (2021)	Cohort, Korea	1,439	adults aged on average 53 years	117 item FFQ	incident COPD cases defined by spirometry	5 years	A decreased intake of dietary fiber, vitamin C, and folic acid is associated with a newly developed airflow limitation
Asthma and related symptoms, lung function							
Saeed et al. (2020)	Cross-sectional, US, NHANES	13,147	adults aged 20–79 years (mean age 46 years)	two-intervieweradministered 24 h recalls	self-reported asthma, wheeze, cough, phlegm production, blood CRP	N/A	High-fiber diet may mediate an inflammatory response and decrease odds of having asthma, especially for women and specific racial groups, cough, wheeze, and phlegm production when compared with low-fiber diet
Lee et al. (2021)	Cross-sectional, Korea, Korean NHANES	10,479	adults aged 19 years and older (mean age 51 years)	63-item FFQ	self-reported asthma, self-reported rhinitis plus nasal endoscopy, serum IgE and specific IgE levels	N/A	As dietary fiber intake increased, the prevalence of asthma (Q4 adjusted odds ratio (OR): 0.656; p for trend < 0.0001) decreased

Table 1 (continued)

References	Study design, Contry, Cohort	n	Population	Dietary fiber measure	Outcome Assessment	Follow up	Main finding
Andrianasolo et al. (2019)	Cross-sectiona, France, NutriNet-Sante Study	35,380	adults aged 18 years and older (mean age 53 years in women, 59 years in men)	three self-administered web-based 24 h dietary records	self-reported asthma symptom score, asthma control test	N/A	Higher intake of total, soluble, insoluble fibres from cereals, fruit and seeds were significantly negatively associated with the asthma symptom score both among women and men; OR for the highest quintile of total dietary fibre compared with the lowest quintile were 0·73 (95% CI 0·67, 0·79) in women and 0·63 (95% CI 0·55, 0·73) in men
Berthon et al. (2013)	Case–control, Australia	137 cases with asthma, 65 contorls	adults aged 18 years and older (mean age 53 years)	186-item semi-quantitative FFQ	asthma severity, lung function (eNO, spirometry, sputum cells)	N/a	Individuals with severe persistent asthma in the subgroup have a high-fat and low-fiber diet compared to healthy controls. This is associated with lower lung function and increased airway inflammation

ARIC atherosclerosis risk in communities, *COPD* chronic obstructive pulmonary disease, *eNO* exhaled nitric oxide, *HFD* high-fiber diet, *FEV1* forced expiratory volume in 1 s, *FFQ* food frequency questionnaire, *LSC* Lovelace smokers cohort, *N/A* not applicable, *NHANES* National health and nutrition examination survey, *OR* odds ratio, *VSC* Veteran smokers cohort

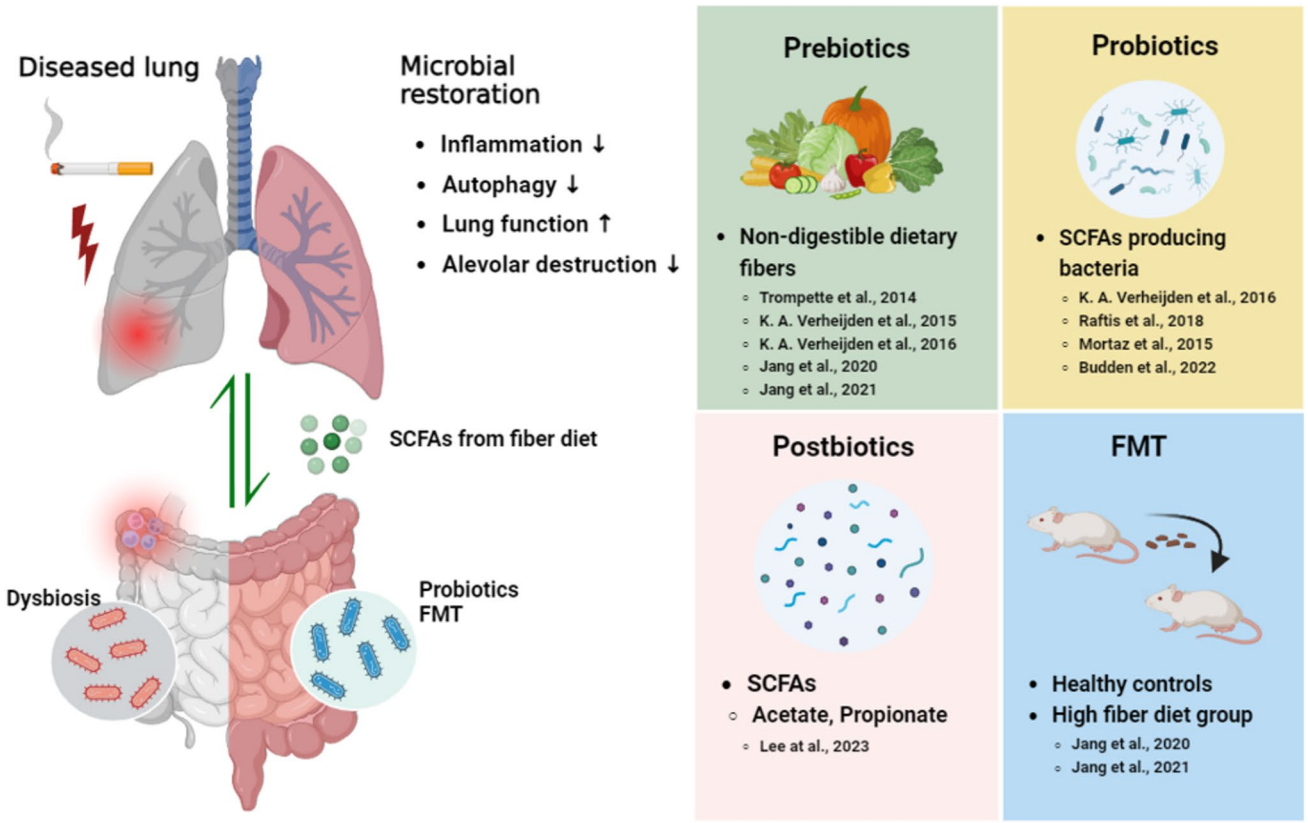

Fig. 1 Therapeutic implications of microbiome modulation in emphysema. *FMT* fecal microbiota transplantation, *SCFAs* short-chain fatty acids. Created with BioRender.com

with propionate alone decreased the $CD3^+$ $CD4^+$ IL-17^+ T-cell population in the lung and spleen (Lee et al., 2023). In contrast, antibiotic-induced microbial dysbiosis aggravated emphysema due to smoking exposure, which is associated with dysregulated inflammation and autophagy. Interestingly, SCFA administration reversed emphysema aggravation, showing reduced inflammatory and autophagy markers, such as inflammatory cells, IL-6, interferon-γ, LC3B, atg3, and atg7 (Kim et al., 2023a). In a near future, genetically modified probiotics secreting some beneficial molecules will be also utilized to treat chronic respiratory diseases (Kim et al., 2023b).

Although the preclinical studies appear promising, further studies are needed to establish a causal relationship. Moreover, how a specific intervention affects not only the disease but also changes in the composition of the lung or gut microbiome should be investigated. Large-scale clinical trials are crucial to demonstrate the effectiveness of new interventions, address patient and time heterogeneity, and elucidate the optimal timing for intervention before implementation in clinical practice.

Future Perspectives & Conclusions

Recent studies elucidated the importance of the microbiome in the regulation of various human biological phenomena. In this context, microbiome modulation techniques constitute an emerging and promising area for developing new treatments, especially for those diseases without appropriate treatment modalities. Chronic respiratory diseases, such as COPD and emphysema, are among such kind of diseases for which several evidence has already shown improvements through gut microbiota modulation and metabolite administration in human-relevant animal models. Further studies on microbial modulation for regulating immunity and potentiating conventional pharmacotherapy will support microbiome manipulation techniques as a new therapeutic area in chronic respiratory diseases.

Acknowledgements This study was supported by grants from the National Research Foundation of Korea (NRF) (No. 2020R1A2C1008431, 2023R1A2C2006688, and RS-2023-00222687, SWL) and the Bio & Medical Technology Development Program of the NRF (No. 2022M3A9G8017220), both funded by the Korean government (MSIT).

Table 2 Preclinical studies on the modulation of chronic airway diseases by microbiomes

References	Model	Type of intervention	Route of administration	Main finding
Allergic airway model				
Trompette et al. (2014)	Murine, HDM, IN	Prebiotic fiber	Diet modification	A low-fiber diet increased the severity of allergic airway inflammation
		Fermentable fiber, pectin		A HFD decreased susceptibility to allergic airway inflammation
				Decreased inflammatory cell infiltration in BALF and lung tissue Decreased IL-4, IL-5, IL-13, and IL-17A mRNA expression in lung tissues
		SCFAs	Drinking water supplementation	Mice treated with propionate were protected against the development of allergic airway inflammation
		Acetate or propionate		Reduction in the total number of cells and eosinophils in BALF Decreased IL-4, IL-5, and IL-17 concentrations
				Decreased IL-13 mRNA expression in the lung
Verheijden et al. (2015)	Murine, HDM, IN	Prebiotic fiber	Diet modification	Th2-related cytokine and chemokine concentrations in the lung were controlled as effectively as with a budesonide treatment
		GOS		AHR development was prevented, as determined through methacholine tests
Verheijden et al. (2016)	Murine, HDM, IN	Prebiotic fiber and probiotics	Diet modification	Symbiotic dietary supplementation can affect respiratory allergic inflammation induced by HDM
		Non-digestible oligosaccharides		Decreased eosinophil and lymphocyte influx in BALF
		Non-digestible oligosaccharides + *Bifidobacterium breve* M-16 V (BB)		Decreased IL-6, IFN-γ, IL-4, and IL-10 concentrations
Raftis et al. (2018)	Murine, HDM, SC, IN	Probiotics	Oral gavage	*B. breve* strain MRx0004, isolated from the gut microbiome of a healthy human, can reduce both neutrophilic and eosinophilic infiltrations
		B. breve strain MRx0004		Decreased proinflammatory cytokines and chemokines involved in neutrophil migration in lung tissues
				Increased lung CD4 + CD44 + cells and CD4 + FoxP3 + cells, Reduced activated CD11b + dendritic cells

Table 2 (continued)

References	Model	Type of intervention	Route of administration	Main finding
Emphysema model				
Mortaz et al. (2015)	Human monocyte cell line THP-1	Probiotics		Suggested usefulness as anti-inflammatory agents in CS-associated disease
	CSE	*Lactobacillus rhamnosus* and *B. breve*		Reduced ability of CS to induce the expression of IL-1β, IL-6, IL-10, IL-23, TNFα, and CXCL-8, as well as HMGB1 release
Jang et al. (2020)	Murine, CS with poly(I:C)	FMT	Oral gavage	FMT or HFD attenuated CS-induced severity of emphysema, decreased cell apoptosis
		Prebiotic fiber	Diet modification	Reduced structural lung destruction by MLI
		20% cellulose or 10% cellulose + 10% pectin		Reduced levels of IL-6 and IFN-γ in BALF and serum
		FMT + HFD	Oral gavage + diet modification	Reduced mRNA levels of IL-1β, IFN-γ, MMP-12, IRF-5, and cathepsin S in lung tissues of both FMT- and HFD-treated mice
		SCFAs Acetate, propionate, and butyrate	Drinking water supplementation	SCFAs were less effective than a prebiotic HFD
Jang et al. (2021)	Murine, CS with poly(I:C)	Prebiotic fiber	Diet modification	Both attenuated the pathological changes associated with emphysema progression and the inflammatory response in CS-exposed emphysema mice
		20% non-fermentable cellulose		Decreased IL-1β, INF-γ, MMP-12, TNFα expression in lung tissues
		20% fermentable pectin		Different types of dietary fiber could modulate the diversity of gut microbiota and differentially impacted anabolism
Budden et al. (2022)	Murine, CS with poly(I:C)	Probiotics	Gavage	Administration of *B. longum* subsp. *longum*, irrespective of its acetate-producing capacity, alleviated cigarette smoke-induced inflammation
		Bifidobacterium longum subsp. *longum* (WT)		Decreased CS-induced cytokines, such as TNFα, CCL8, and CXCL2, in lung tissues
		Bifidobacterium longum subsp. *longum* with impaired acetate production capacity (MUT)		Reduced expression of adhesion factors, such as VCAM1 and ICAM1, in lung tissues
Lee et al. (2023)	Murine, CS with poly (I:C)	Postbiotics Acetate or propionate	Drinking water supplementation + IP	Reduced alveolar destruction and the production of proinflammatory cytokines in lung tissues Propionate treated group showed decreased CD3 + CD4 + IL-17 + T-cell population in the lung and spleen

AHR airway hyperresponsiveness, *BALF* bronchoalveolar lavage fluid, *CS* cigarette smoking, *CSE* chronic smoking extracts, *FMT* fecal microbiota transplantation, *HDM* house dust mite extract, *GOS* galactooligosaccharides, *HFD* high-fiber diet, *IN* intranasal administration, *MLI* mean linear intercept; *MUT*, mutant; poly(I:C), polyriboinosinic:polyribocytidylic acid *SC* subcutaneous injection, *SCFAs* short-chain fatty acids, *WT* wild type

We would like to thank Editage (www.editage.co.kr) for English language editing.

Declarations

Conflict of Interest No author received an honorarium, grant, or any other form of payment to produce the manuscript. The study was not commissioned, and no commercial agency was involved in any aspect of this study. The authors have no other competing interests to declare.

Ethical approval As this is a minireview and does not involve original research with human subjects, no ethics statement was required (Hanson et al., 2016; Kim et al., 2020; Leng et al., 2017; Root et al., 2014; Varraso et al., 2010).

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