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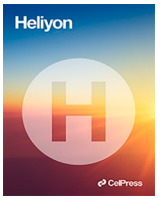

Review article

The role of gut-lung axis in COPD: Pathogenesis, immune response, and prospective treatment

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and healthcare burden worldwide. The progression of COPD is a combination of genetic predisposition and environmental factors, primarily cigarette smoking, and the underlying mechanisms are still unknown. Intestinal microecology impacts host immunity, metabolism, and resistance to pathogenic infections, which may be involved in pulmonary disease. Moreover, substantial interaction occurs between the intestinal and respiratory immune niches. After reviewing nearly 500 articles, we found the gut-lung axis plays an important role in the development of COPD. COPD patients often have dysbiosis of the intestinal microenvironment, which can affect host immunity through a series of mechanisms, exacerbating or protecting against COPD progression. This paper summarizes how the gut-lung axis influences COPD, including the alterations of intestinal microecology, the pathological mechanisms, and the involved immune responses. Finally, we summarize the latest research advances in COPD treatment from the perspective of regulating the gut-lung axis and intestinal immunity and evaluate the potential value of the gut-lung axis in improving COPD prognosis.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease with major pathological changes including chronic airway inflammation and progressive decline in lung function. COPD affects nearly 400 million people worldwide, and its incidence continues to rise every year, accounting for a huge socioeconomic burden [1]. The pathogenesis of COPD is not well understood and possible causes include cigarette smoke exposure, genetic predisposition, social and environmental factors, etc.

The gut microenvironment dysbiosis plays an important role in the development of COPD. Gut microecology is the microbial community of gut microbiota, including symbiotic and pathogenic microorganisms present in tissues and the lumen. Ecological dysbiosis of the gut microbiota can affect the body's immune balance and associated with diseases in multiple systems, including obesity, diabetes, atherosclerosis, and nonalcoholic fatty liver disease. The lung microenvironment is likely to be affected by change of

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gut microbiota, since microbiomes also exists in the upper and lower respiratory tract. Respiratory diseases are often accompanied by gastrointestinal symptoms, and people with gastrointestinal disorders also have respiratory manifestations. For example, patients with influenza virus infection have concomitant gastrointestinal symptoms [2], while patients with inflammatory bowel disease (IBD) have gut microbiota alterations, and up to 50% of IBD patients have decreased pulmonary function [3]. This bidirectional communication between the gut and lung is called the gut-lung axis.

The gut-lung axis plays an important role in respiratory diseases. COPD often coincides with chronic gastrointestinal diseases, and COPD patients are 2–3 times more likely to be diagnosed with IBD than healthy individuals [4]. Similarly, people with IBD may have a higher risk of COPD compared to healthy ones. In the two subtypes of IBD, Crohn's disease and ulcerative colitis, the odds ratio for COPD is 2.72 and 1.83, respectively [5]. The gut-lung axis can influence COPD development through the migration of immune cells, destruction of mucosal immunity, and changes in cytokines in the gut and lung microenvironment, etc.

Previous research studied the change of gut microbiota in COPD, but research was rather separated and a research gap exists between the theory of gut-lung axis and the clinical management of COPD. Therefore, there's a need to summary the relevant studies in the gut-lung axis and their association with COPD to better improve the management of disease prognosis. In this review, we discuss the mechanisms of the gut-lung axis in COPD and highlight the recent advances in COPD treatment from modulating the gut-lung axis,

Table 1
Alterations of gut microbiota in COPD progression.

Study	Origin	Sample	Methods	Enriched microbes	Depleted microbes
Animal and laboratory evidence					
Tomoda, 2011 [S1]	Rat	Cecal contents	Selective isolation by specific algar, microscopic bacterial counts	/	*Bifidobacterium* sp.
Wang, 2012 [S2]	Mice	Cecal contents	qPCR, 16S rRNA gene sequencing	*Clostridium* sp.	*Lactococcus, Ruminococcus, Enterobacteriaceae.* and segmented filamentous bacteria
Allais, 2016 [S3]	Mice	Colonic sample	Illumina sequencing, gradient gel electrophoresis	*Lachnospiraceae* sp.	/
Dubois-deruy, 2020 [S4]	Mice	Cecal samples	16S rRNA gene sequencing	*Deferribacteres phylum* (in all), *Clostridiaceae* (in obese mice)	*Actinobacteria* (particularly *Bifidobacteria*),
Bai, 2022 [S5]	Mice	Fecal sample	Shotgun metagenomic sequencing, liquid chromatography	*Eggerthella lenta*	*Parabacteroides distasonis*, *Lactobacillus* spp.
Healthy smokers					
Benjamin, 2012 [S67]	Human	Fecal sample	Fluorescent in situ hybridization	*Bacteroide (Prevotella), Bifidobacteria,*	*F. prausnitzii*
Biedermann, 2014 [S68]	Human	Fecal sample	Oligonucleotide probes targeting rRNA and FISH analysis	*Firmicutes (Clostridium coccoides, Eubacterium rectale), Actinobacteria* (HGC bacteria and *Bifidobacteria*),	*Bacteroidetes (Prevotella* spp. *and Bacteroides* spp.*), Proteobacteria (β- and γ-subgroup of Proteobacteria)*
Ishaq, 2018 [S69]	Human	Fecal sample	PCR-gradient gel electrophoresis, 16S rRNA gene sequencing	*Bacteroides vulgatus*	*Lactobacillus, Bifidobacterium, Clostridium leptum* subgroup
Shanahan, 2018 [S70]	Human	Intestinal tissue	16S rRNA gene sequencing	*Firmicutes* sp.*; Streptococcus, Rothia, and Veillonella*	*Bacteroidetes* sp*, Actinobacteria* sp.*, and Prevotella*
McLean, 2019 [S71]	Human	Fecal sample	16S rRNA gene sequencing	*Ruminococcus, Akkermansia, Firmicutes, Bacteroides* and *Staphylococcus*	/
Nolan-Kenney, 2020 [S72]	Human	Fecal sample	16S rRNA gene sequencing	*Catenibacterium, Peptostreptococcaceae, Mitsuokella, Slackia, Collinsella, Alphaproteobacteria*	/
Harakeh, 2020 [S73]	Human	Fecal sample	16S rRNA gene sequencing by Miseq technology	*Lactobacillus amylovorus, B. thetaiotaomicron*	*Fusobacteria* and *Tenericutes*
Prakash, 2021 [S74]	Human	Fecal sample	16S rRNA gene sequencing	*Veillonellaceae, Prevotella*	*Lachnospira*
COPD patients					
Deng, 2021 [10]	Human	Fecal sample	16S rRNA gene sequencing	/	*Bifidobacteria and Lactobacilli*
Brennan M [13]	Human	Fecal sample	16S rRNA gene sequencing	*Haemophilus and Aspergillus*	*Streptococcus*
Bowerman, 2020 [S75]	Human	Fecal sample	16S rRNA gene sequencing, metagenomics	*Bifidobacteriaceae, Eubacteriaceae, Lactobacillaceae, Micrococcaceae, Streptococcaceae* and *Veillonellaceae*	*Desulfovibrionaceae, Gastranaerophilaceae, Selenomonadaceae, Bacilli* and *Clostridia*
Sun, 2020 [S76]	Human	Fecal sample	16S rRNA gene sequencing, PCR	*Clostridia, Firmicutes, Ruminococcaceae*	*Proteobacteria, Enterobacteriales*
Li, 2021 [S77]	Human	Fecal sample	16S rRNA gene sequencing, SCFA analyses	*Firmicutes, Prevotellaceae, Ruminococcaceae*	*Bacteroidetes*
Liu, 2022 [S78]	Human	Fecal sample	Shortgun metagenomes sequencing	*Faecalicatena, Oscillibacter, Lawsonibacter, Flavonifractor*, and *Streptomyces*	*Lachnospira, ER4, KLE1615, Eubacterium_F*, and *Coprococcus*

to evaluate the value of the gut-lung axis for the prevention and treatment of COPD.

2. The cause-and-effect of intestinal microecology on COPD

2.1. Smoking and COPD induce the alterations of intestinal microenvironment

Smoking is a significant causal factor of COPD. Cigarette smoke not only exacerbates the inflammatory response in the lung but also triggers dysbiosis of the intestinal microenvironment. The harmful chemicals present in tobacco smoke initiate inflammatory responses within the respiratory system, damaging the airway epithelium over time, which leads to airflow limitation and the characteristic symptoms of COPD. Furthermore, smoking exacerbates COPD symptoms and accelerates the decline in lung function. Smoke exposure can lead to the formation of biofilm in specific genera of bacteria, enhancing their adhesion to gut epithelium and increasing their abundance, such as *Streptococcus* [6]. Cigarette smoke also increases the permeability of the intestinal and pulmonary mucosa and

Table 2
Microbially-derived substance and related gut microbes that play protective roles in COPD.

Study	Subjects	Substance	Related microbes	Potential mechanism	Effect in the lung
Tomoda, 2015[S6]	Female C57BL/6 mice	SCFA	Intestinal microflora produces organic acids	↓total cell and macrophage counts; ↓lymphocyte and neutrophil counts in BALF	Result in anti-inflammatory effect in the lungs; suppress elastase-induced emphysema
Trompette, 2018[S7]	BALB/c or C57BL/6 mice	SCFA	Intestinal microbiota that ferments dietary fiber	↓CXCL1 production, thus reduce neutrophil recruitment to the airways; ↑CD8+T cell effector function	Promote the resolution of respiratory infection while preventing immune-associated pathology
Jang, 2021 [S8]	Female C57BL/6 mice	SCFA, dietary fibers	*Lactobacillaceae, Defluviitaleaceae*, and *Oscillospiraceae*	Modulate the microbial community structure	Improve alveolar destruction and inflammation during emphysema progression
Budden, 2022[S9]	Female C57BL/6 mice	SCFA	*Bifidobacterium longum* subsp. *longum*	↓leukocytes, neutrophils and macrophages; ↓acetate production; ↓smoke-induced butyrate depletion	Attenuate parenchymal inflammation; alleviate smoke-induced lung inflammation
Hildebrand, 2023[S10]	Male C57BL/6JRj mice	SCFA	*Bifidobacterium, Faecalibaculum*, and *Lactobacillus*	↓oxidative stress; ↓metabolic alteration; ↑inflammatory signaling	↑activation of myeloid cells in the lungs; reduce pulmonary inflamm-aging
Wang, 2023[S11]	Male Sprague-Dawley rats	SCFA	*Ruminococcaceae, Christensenellaceae*, and *Aerococcaceae*	↑ZO-1 and occludin-1 in the intestine; ↓TNF-α, IL-8, IL-6, and IL-17 in the lung; ↓infiltration of inflammatory cells	Strengthen the intestinal barrier function; improve pulmonary function; inhibit the inflammatory response
Richards, 2020[S12]	16HBE Cells	SCFA	/	↓IL-4-induced IL-6 production; ↑tight junction protein ZO-1 expression	Enhance the barrier function of HBE cells; induce airway epithelial cells recovery after stimuli exposure
Lai, 2022[S13]	C57BL/6 mice	LPS	*Parabacteroides goldsteinii*, Pg bacterial strain MTS01	↓proinflammatory cytokines; ↓BALF cellular infiltration; ↑cellular ribosomal and mitochondrial activity	↓lung inflammation; ameliorate cigarette smoke-induced COPD
Kolling, 2018[S14]	Male Swiss-albino mice	Peptidoglycan	*Lactobacillus rhamnosus* and *L. plantarum*	↑Th2 response; ↑the recovery of B cells; ↑the concentration activity of anti-pneumococcal antibodies	Resistance to pneumococcal infection; reduced cell infiltration in the lung parenchyma
Bowerman, 2020 [20]	Human stool sample	Phytohemagglutinin (PHA)	*Bifidobacteriaceae, Eubacteriaceae, Lactobacillaceae, Micrococcaceae, Streptococcaceae and Veillonellaceae*	↓airway inflammation ↑function of gut mucosal barrier	Restore the balance of gut microenvironment, and protective against COPD exacerbation
Vareille, 2019[S15]	C57BL/6J mice	PHA	*L. plantarum* CIRM653	Induce immunosuppressive T cell response; prevent innate cell recruitment and cytokine production in the lungs	Reduce the proinflammatory response induced by *K. pneumoniae* in airway epithelial cell lines
Markhijia, 2014[S16]	Male Balb/c mice	trimethylamine-N-oxide (TMAO)	*Clostridium spp.*	Reduce AHR, inflammation, mucus metaplasia, and collagen deposition	Attenuate ER stress; inhibit airway remodeling and lung inflammation

*↑means increase or upregulate; ↓means decrease or downregulate.
Abbreviations: AHR, airway hyper reactivity; BALF, bronchoalveolar lavage fluid; ER, endoplasmic reticulum; HBE cells, human bronchial epithelial cells; LPS, lipopolysaccharide; SCFA, short chain fatty acid.

weakens immune defense. Rats exposed to cigarette smoke for 6 months show intestinal mucosal barrier dysfunction and structural alterations, including neutrophil infiltration, epithelial detachment, reduced expression of tight junction proteins occludin and ZO-1, and elevated levels of interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) [7]. In mice, chronic smoke exposure results in increased intestinal permeability prior to the onset of emphysematous lung pathology [8].

Similar to smokers, alterations in the lung and gut microbiota also occur in COPD patients (Table 1). Smoking disrupts the balance of lung microbiota, favoring harmful bacteria over beneficial ones, leading to increased susceptibility to infections and worsening of COPD [9]. The interaction between lung and gut microbiota is bidirectional, with alterations in one affecting the other. This interplay, mediated by shared immune signaling pathways, such as cytokine signaling and toll-like receptor activation, as well as neuroendocrine pathways, such as the hypothalamic-pituitary-adrenal axis and the vagus nerve-mediated communication has implications for respiratory and gastrointestinal health. Studies have shown associations between gut dysbiosis and changes in lung microbiota composition, as well as the impact of lung microbiota disruptions on gut health [10]. In the stool of patients with stable COPD, the level of beneficial bacteria significantly decreased, such as *bifidobacteria* and *lactobacilli* [11]. Analysis of gut microbiota in COPD patients with different GOLD grades also revealed some correlations between severity and microbiota pattern: in COPD with GOLD 1, the abundance of *Bacteroides* was higher, and the abundances of *Tyzzerella 4* and *Microbacterium* spp. Were lower; in patients with GOLD 2–4, the abundance of *Ruminococcaceae* and *Lachnoclostridiu*m reduced; and *Clostridium* and *Aerococcus* were more abundant in COPD of GOLD 3 and 4 [12].

COPD patients are more susceptible to respiratory infections, which is the most important factor in COPD exacerbation. Acute exacerbation of COPD (AECOPD) refers to a worsening cough and dyspnea compared to the usual condition, or with increased sputum and other events that require changes in medication regimen. Compared to stable COPD, AECOPD patients have increased intestinal permeability and dysbiosis of the intestinal microenvironment. Similarly, in the feces of AECOPD patients, the gut microbiota abundance was significantly altered with reduced diversity [13]. In AECOPD patients, the level of *Streptococcus parapsilosis*_B increase

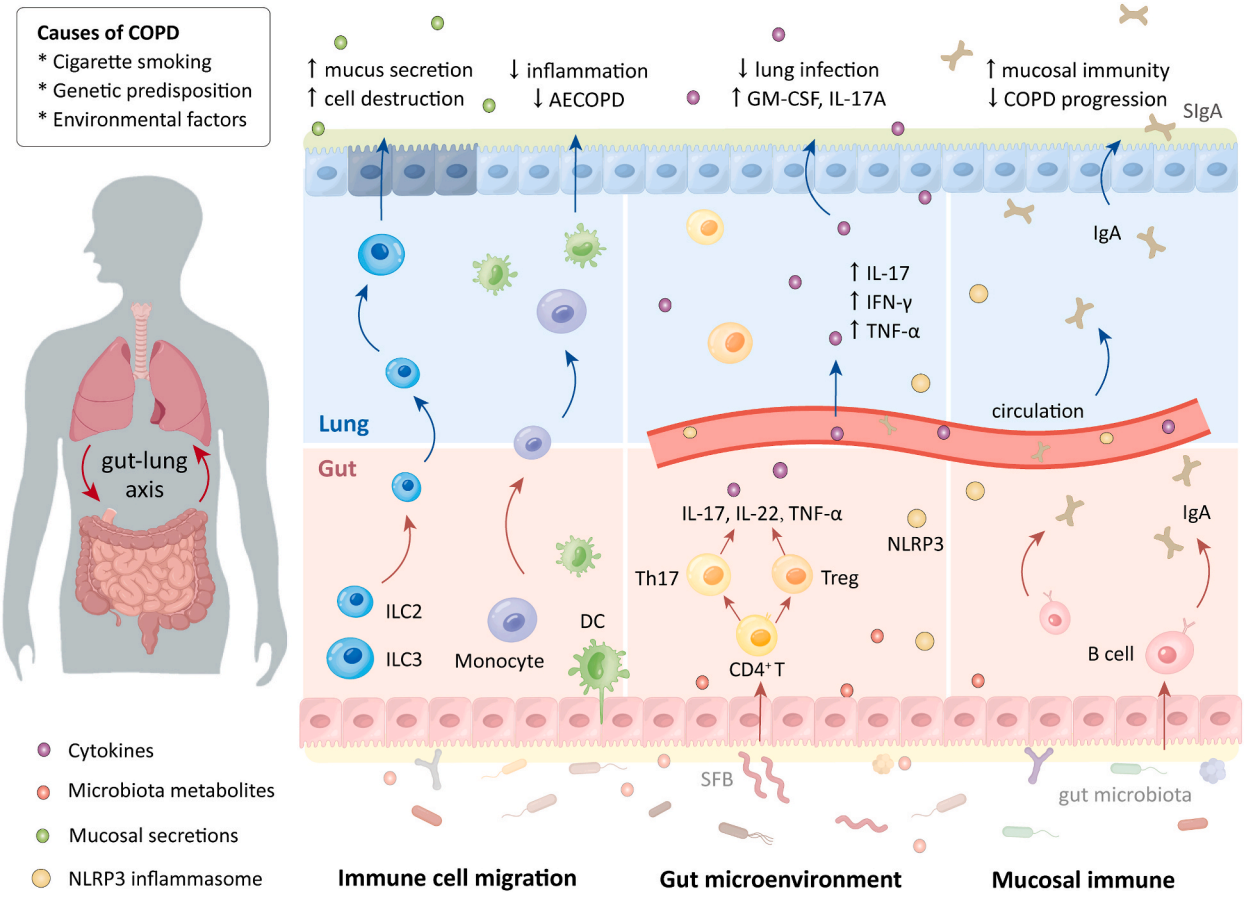

Fig. 1. Mechanism of the gut-lung axis in the progression of COPD. The mechanism of the gut-lung axis in COPD includes immune cell migration, gut microenvironment alteration, and changes in the mucosal immune. The migration of ILC2 and ILC3 may destroy the airway epithelial cells and increase the mucus secretion in the alveolar, accelerating COPD progression; while migration of DC and monocyte can reduce pulmonary inflammation. Change in the gut microenvironment triggers the release of cytokines like IL-17 and TNF-α, which circulate from gut to lung and reduce infection risk. Gut microbiota also stimulates B cell to produce IgA through mucosal immune, enhance the lung mucosal immunity, and slow down COPD progression.

in the sputum, whereas increases in both *Streptococcus parapsilosis*_B and *Streptococcus salivarius* are observed in feces [14]. Studies have demonstrated significant dysregulation of the intestinal microecology in smoking, stable COPD and AECOPD. The altered microbiota and their metabolites will in turn change the lung function and regulate COPD progression.

2.2. Components and metabolites of intestinal microbes modulate the progression of COPD

A healthy gut microbiota participates in host immunity through microbial composition and metabolites, maintaining homeostasis. Alterations of the gut microbiota can impact pulmonary immune function. The soluble components and metabolites of the microbiota play important role in the crosstalk between the gut and lung immune response, which may contribute to COPD progression.

Soluble components of the gut microbiota, such as lipopolysaccharide (LPS), can regulate intestinal immunity, including increasing cytokine levels, recruiting neutrophils and macrophages, and enhancing humoral immunity. These components also have anti-inflammatory effects, such as polysaccharide A (PSA) of *Bacteroides fragilis*, which inhibits the intestinal inflammatory response [15]. Short-chain fatty acids (SCFA) are important metabolites of the gut microbiota with anti-inflammatory effects. Three main SCFAs are acetate, propionate, and butyrate, of which acetate and propionate are produced by *S. fragilis* and butyrate by *S. firmicutes* [16]. SCFAs are main metabolites of gut microbiota through fermenting dietary fibers, which can impact the lung homeostasis, suggesting that it may migrate from the gut to lung and modulate lung immunity [17]. The two mechanisms of SCFA immunomodulation include driving anti-inflammatory responses by coupling downstream effector molecules and modulating the immune response by inhibiting histone deacetylase activity in cells [18]. SCFA also regulates immunity in extraintestinal organs, promotes anti-inflammatory responses, reduces airway inflammation, and alleviates COPD symptoms [19]. Exposure to cigarette smoke may decrease pulmonary SCFA concentration, accelerating COPD development; Cigarette condensates also reduce SCFA production *in vitro* [20]. Circulation SCFA levels in COPD patients are lower, and the decreased levels correlate with COPD severity [21]. Other metabolites of gut microbiota, like Phytohemagglutinin (PHA) and trimethylamine-N-oxide (TMAO) also involve in COPD by reducing airway inflammation and restoring the epithelial function [22].

Soluble components and metabolites of gut microbiota can play beneficial roles in promoting lung homeostasis, while reducing these substances triggered by risk-factors exposures may accelerate COPD progression (Table 2). Dysbiosis of the gut microbiota is a key factor of COPD exacerbation, including a decrease in beneficial bacteria and their metabolites, an increase in opportunistic pathogenic bacteria such as *Prevotella* and *Escherichia*, and the destruction of homeostasis [23]. Few animal studies have indicated the microbiota that exacerbates COPD, and the exact metabolites remain largely unknown. The overgrowth of pathogenic bacteria can disrupt the homeostasis between the microbiota and host, thus exacerbates COPD.

The next section discusses the biological mechanisms of the gut-lung axis involved in COPD development, including evidence from in vivo and *in vitro* research. Specifically, the effects of immune cell migration, mucosal immune, and immune response of the intestinal microenvironment on COPD is also summarized (Fig. 1).

3. Immune mechanisms of the gut-lung axis in the development of COPD

3.1. The dual effect of intestinal immune cell migration to the lung on COPD progression

One of the main communication pathways of the gut-lung axis is the migration of immune cells between the gut and lung, and intestinal immune activation regulates COPD progression. Lung inflammation in COPD includes the accumulation of immune cells, and disease progression is associated with lymphoid follicles formation and infiltration of immune cells in the airway epithelium and lumen. Some of these cells originate from the intestine and can be activated by intestinal immune responses, prior to migration to the lung [24]. Migration of innate lymphocyte cells (ILCs) along the gut-lung axis may accelerate COPD progression, while migration of monocytes and dendritic cells (DCs) may play protective roles in COPD.

ILCs are particularly abundant in mucosal barriers in the gut and lung, and their migration from gut to lung may induce COPD exacerbation. In COPD patients, the number of ILCs increased significantly in peripheral blood and lung tissue, and a higher ILC1/ILC2 ratio in peripheral blood was positively correlated with disease severity [25]. In COPD mice, gut microbiota interaction with CD103+ CD11b + DCs may induce IL-22+ ILC3 in the gut to express CCR4, which in turn mediates ILC3 migration to the lung [26]. In the lung, the influx of IL-22+ ILC3 can increase the susceptibility of respiratory infection. ILC2 can also migrate from the gut to the lung induced by IL-25, and participate in local immunity, leading to inflammatory transfer from the gut to lung [27]. By interconnecting the circulatory systems of two mice, and injecting IL-25 intraperitoneally into one, the activated ILC2s can migrate from the intestine of one mouse to the lung tissue of both, exacerbating lung inflammation [28].

Migration of monocytes and DCs through the gut-lung axis plays a protective role in COPD. An important feature of lung inflammation in COPD is an increase in macrophages, neutrophils, lymphocytes, and DCs, and there is usually an overactivation of Th2 cells. SCFA in the gut may induce the production and maturation of monocytes, which migrate partially to the lungs after maturation, differentiate into DCs, inhibit naive T cells to differentiate into Th2 cells, and reduce the proportion of Th2 in the lungs [29]. In *H. capsulatum*-infected mice, tumor necrosis factor inhibitors induce migration of intestinal CD11b + CD103+ DCs to the lung, increase the number of Treg cells, reduce the level of inflammatory factors, and protect against pulmonary fungal infections [30].

In the landscape of COPD, characterized by its heterogeneity, the emerging recognition of Th2 inflammation presents a compelling avenue for exploration. This expanding understanding underscores the intricate interplay between the gut and lung ecosystems, as governed by the gut-lung axis. Within this context, elucidating how the intestinal microecology differentially modulates the diversified inflammatory responses in COPD assumes paramount significance [31]. By dissecting the mechanisms through which gut microbial

components and metabolites exert influence on Th2-mediated inflammation, we gain crucial insights into the pathogenesis of COPD and potential therapeutic targets [32].

3.2. Disruption of mucosal immunity induces and exacerbates COPD

Similarities exist between the intestine and respiratory tract in epithelial origin, anatomical structure, and biological colonization. Both intestinal and airway mucosa are derived from the endoderm with microvilli (intestine) or ciliated protrusions (respiratory tract), and serve as sentinels of the human immune system. Under physiological conditions, the main flora of the two sites is similar, including *Bacteroidetes*, *Firmicutes*, and *Aspergillus* [33]. Functional similarities also exist between intestinal and airway mucosa, and intestinal and airway tissues express common homing receptors, such as CCL28, CXCL8, and CCR9, on which lymphocytes can rely for inter-tissue migration [34]. Gut microbiota can induce IgA production by B cells, and IgA migrates through the circulatory system to the airway mucosa to deliver immune messages. By supporting mucosal immunity, the gut microbiota reduces the risk of lung inflammation and acts as an important protective mediator against *Streptococcus pneumoniae* infection by enhancing alveolar macrophage function [35].

Patients with COPD usually have an impaired airway mucosal barrier. Cigarette smoke can damage the respiratory epithelial barrier, leading to increased level of epithelial reactive oxygen species (ROS) and increased permeability, which exacerbate COPD [36]. Excessive ROS production leads to a decrease in the antioxidant capacity and affects intestinal immune function. Mechanisms for increased intestinal mucosa permeability include smoking-induced disruption of the intestinal barrier, systemic and gastrointestinal hypoxia, and reduced intestinal barrier function. Exposure to cigarette smoke and reduced antioxidant capacity may reduce blood flow to the intestinal mucosa, leading to chronic hypoxia. Concomitant systemic hypoxemia in COPD patients due to emphysema and hypoventilation disrupts intestinal epithelial cells and increases intestinal mucosal permeability. Disruption of the intestinal mucosal barrier in COPD patients accelerates the deterioration of pulmonary function and increasing the risk of COPD exacerbation [37].

3.3. Alteration in the intestinal microenvironment contributes to COPD progression

Alterations in the intestinal microenvironment can affect pulmonary immunity, leading to the pulmonary microenvironment dysbiosis and decreased lung function, which further worsens COPD. On the one hand, when the intestinal microenvironment is disrupted, cytokines and inflammatory mediators can rise and “overflow” from the gut, promoting lung inflammation through circulation. On the other hand, the activation of NLRP3 inflammasome in the gut contributes to the transfer of gut microbiota to the lung, impacting the lung microenvironment [38].

Cigarette smoke may increase circulating IL-17A and IL-17F levels in both non-COPD and COPD individuals, regulating neutrophil and macrophage inflammation, activating inflammatory responses in the lower respiratory tract that promote COPD development. Commensal gut bacteria, segmented filamentous bacteria (SFB), can protect mice from *Streptococcus pneumoniae* infection by similar mechanism. SFB can induce the production of antimicrobial peptides, secretory immunoglobulin A and pro-inflammatory cytokines [39]. SFB stimulates intestinal Th17 cells to release IL-17 and increases IL-22 levels in the lungs to reduce lung inflammation. The dominant growth of SFB plays a protective role in methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia [40]. In mice with pulmonary infection, GM-CSF and IL-17A are critical for the clearance of *Streptococcus pneumoniae* and *Klebsiella pneumoniae*. Both cytokines can be regulated by oral antibiotic administration, and restoration of gut microbiota can repair the clearance defect of either *Streptococcus pneumoniae* or *Klebsiella pneumoniae* [41]. The intestinal inflammation of COPD also affects the systemic immune response. Intestinal inflammation can lead to elevated production of tumor necrosis factor-α (TNF-α), and the circulating level of TNF-α is strongly correlated with the severity of COPD [42]. TNF-α inhibitors can alleviate inflammation and have significant efficacy in both COPD and intestinal inflammation.

The NLRP3 inflammasome (Nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin-containing domain 3) can act as regulators, promoting recruitment of inflammatory cells and modulating immunity; the gut and lung microbiota can also influence NLRP3 inflammasome function. NLRP3 inflammasomes are associated with the exacerbation of COPD, and their activation mediates the secretion of pro-inflammatory cytokines IL-1β and IL-18. The mRNA levels of NLRP3, cysteine-1, IL-18, and IL-1b were significantly higher in peripheral blood mononuclear cells and bronchial tissues of AECOPD patients compared to non-COPD patients with long-term smoking and were positively correlated with bacterial load in BALF [43]. In contrast, concentrations of all these inflammatory mediators were significantly lower in stable COPD compared to AECOPD patients, and systemic and local activation of NLRP3 inflammatory vesicles may contribute to COPD exacerbation [44].

4. Prospective treatments for COPD based on the gut-lung axis

4.1. Antibiotics

The use of antibiotics is a fundamental strategy in COPD treatment, and AECOPD usually requires empirical antibiotic therapy. The GOLD strategy advocates the use of antibiotics in AECOPD, and it can significantly reduce the mortality and risk of secondary pneumonia in AECOPD patients. Long-term use of antibiotics, especially oral antibiotics, can lead to disruption of the gut microbiota, which affects immune responses and leads to COPD exacerbation. Macrolides are common antibiotics in AECOPD treatment, which is effective in treating the lung infection, especially atypical pathogen infection. In mice with pneumonia, oral antibiotics may impair hematopoiesis and lead to exacerbation of pneumonia. Frequent use of antibiotics may increase the rate of relapse in COPD patients,

and treatment of such patients often needs to be prolonged to maintain the efficacy of antibiotics [45]. Reliance on conventional antibiotics for COPD can lead to dysbiosis of the gut microbiota, which increases the risk of readmission, prolongs the patient's hospital stay, and may further worsen COPD, creating a vicious cycle. Therefore, patients with COPD, especially those with infection, should be treated with complementary treatments in addition to conventional antibiotics [46].

4.2. Dietary supplements

Dietary supplement is an important complementary therapeutic approach in COPD, which mainly involve oral probiotics and dietary fiber. Probiotics are a group of beneficial active microorganisms and can help maintain or restore the homeostasis of the gut, which exert systemic anti-inflammatory effects, thereby relieving COPD symptoms. Oral administration of *Lactobacillus garciae* or *Lactobacillus rhamnosus*, can stimulate the pulmonary immune response, protect COPD mice from pneumococcal infection, and prevent COPD exacerbation [47]. Gavage supplementation with *Lactobacillus rhamnosus* and *Bifidobacterium shortum* may reduce pulmonary inflammation and damage of bronchial epithelial cells in COPD mice [48]. Both probiotics also show similar anti-inflammatory effects on cigarette smoke-induced macrophage inflammation *in vitro*, and intestinal supplementation with both bacteria may treat COPD through anti-inflammatory effects. Patients with chronic pneumonia showed significant improvement in lung function (FEV1/FVC) after 6 weeks of oral probiotic administration compared to placebo [49]. In COPD patients, oral probiotics can alleviate COPD symptoms by inducing the expression of certain cytokines like IL-6, TNF-α, and CXCL-8 and suppressing macrophages inflammation in the gut [50].

Dietary fiber is also a common dietary supplement for COPD patients, and its main component, SCFA, is protective against COPD. Diets high in SCFA may prevent elastase-induced pulmonary inflammation and emphysema. Diets high in dietary fiber can alleviate symptoms in COPD patients, and are associated with reduced prevalence of COPD in populations [51]. Increased intake of fruits and vegetables may improve symptoms (e.g., dyspnea) in COPD patients and may also reduce the prevalence of COPD in the population.

4.3. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a therapeutic method to change the recipient's gut microbiota by normalizing the composition through transplanting stool. FMT can reshape the intestinal microenvironment and has been widely used in the treatment of various gastrointestinal diseases. FMT may serve as a potential treatment for lung diseases by regulating lung inflammation through the gut-lung axis [52]. In COPD mice, FMT improves abnormal amino acid metabolism in serum and *F. aureus* LPS antagonizes *E. coli* LPS-induced inflammation, reducing intestinal and pulmonary inflammation and alleviating COPD symptoms. FMT can also modulate the gut microbiome in emphysematous mice, inhibit inflammatory responses and cell apoptosis, slow emphysema development, and improve COPD prognosis. In smoke-induced COPD mice subjected to FMT, the commensal bacterium *Parabacteroides goldsteinii* isolated from feces alleviates the symptoms of COPD by inhibiting the toll-like receptor 4 (TLR4) pathway, suppressing inflammatory response in the gut and lung, and enhancing cellular mitochondrial activity [53].

Clinical trials have demonstrated that various gastrointestinal diseases such as IBS, IBD, and obesity can be effectively treated by FMT [54]. Although FMT has been less studied in respiratory diseases, based on the theory of the gut-lung axis, FMT may become an effective option for the treatment of COPD patients.

4.4. Traditional Chinese medicine and herbal formula

The application of traditional Chinese medicine to regulate intestinal microecology can improve COPD symptoms, and reduce the risk of COPD progression. *In vivo*, herbal medicines such as Qibai Pingfei Capsules, Tonifying Lung and Kidney Soup can improve lung function by activating a series of pathways such as STAT3/STAT5, and Xuanbai Chengqi Decotion can ameliorate lung inflammation in COPD mice by correcting the Th17/Treg imbalance in the gut-lung axis [55,56]. Tonifying Lung and Spleen Soup could remodel the SCFAs/GPR43/NLRP3 pathway by reshaping the gut microbiota, repairing the broken mucosal barrier, and improving mucosal immune function in COPD rats [57]. In a population study of COPD, oral administration of Caoshi silkworm granule compound improved the SGRQ score (St. George's Respiratory Questionnaire) in patients with stable COPD and improved lung function in COPD patients [58].

While traditional Chinese medicine (TCM) holds promise in regulating intestinal microecology to improve COPD symptoms and mitigate disease progression, it's crucial to consider safety aspects and potential side effects associated with such treatments, as caution is warranted as these treatments may have adverse effects or herb-drug interactions. For instance, Xuanbai Chengqi Decotion, while ameliorating lung inflammation in COPD mice, may exert effects on the gut-lung axis that need further elucidation regarding long-term safety. Similarly, Tonifying Lung and Spleen Soup's remodeling of the SCFAs/GPR43/NLRP3 pathway in COPD rats underscores potential benefits but also raises concerns about unintended consequences. Moreover, while population studies like the one involving Caoshi silkworm granule compound show promising outcomes in improving COPD symptoms and lung function, careful monitoring of adverse reactions and standardized safety protocols are imperative to ensure the overall well-being of patients undergoing TCM treatments for COPD management [58].

5. Conclusions and prospects

The gut-lung axis is disrupted in and impacts the COPD development through alterations in the gut microbiota and immune

microenvironment. Changes in intestinal microecology and lung pathogenesis are closely related and can affect COPD progression through a range of mechanisms, such as immune cell migration and regulation of the immune microenvironment. This review summarizes the role of the gut-lung axis in the development of COPD, including the association between COPD and changes in the gut microenvironment, biological mechanisms of the gut-lung axis, and potential COPD treatments that target the gut-lung axis.

Long-term inhalant therapy is the cornerstone of the COPD treatment strategy. This strategy should be complemented by multifaceted management, including counseling and pharmacotherapy for smoking cessation, pulmonary rehabilitation, treatment of comorbidities, influenza and pneumococcal immunizations, and prescription of long-term oxygen therapy for hypoxic patients. Modulation of intestinal microecology through oral dietary supplements and fecal transplantation to regulate the intestinal microenvironment can provide effective complementary treatment for COPD patients (Fig. 2). These promising treatments may help reduce complications and improve COPD prognosis. Further elucidation of the role of the gut-lung axis in COPD will bring new understanding of the pathological mechanisms and novel therapeutic options for COPD treatment, as well as a comprehensive approach to prevention, holistic management, and improved prognosis and quality of life for COPD patients.

Questions for future research

- Which additional gut microbiota contribute to the development of COPD beyond those identified in the tables outlined in this review?

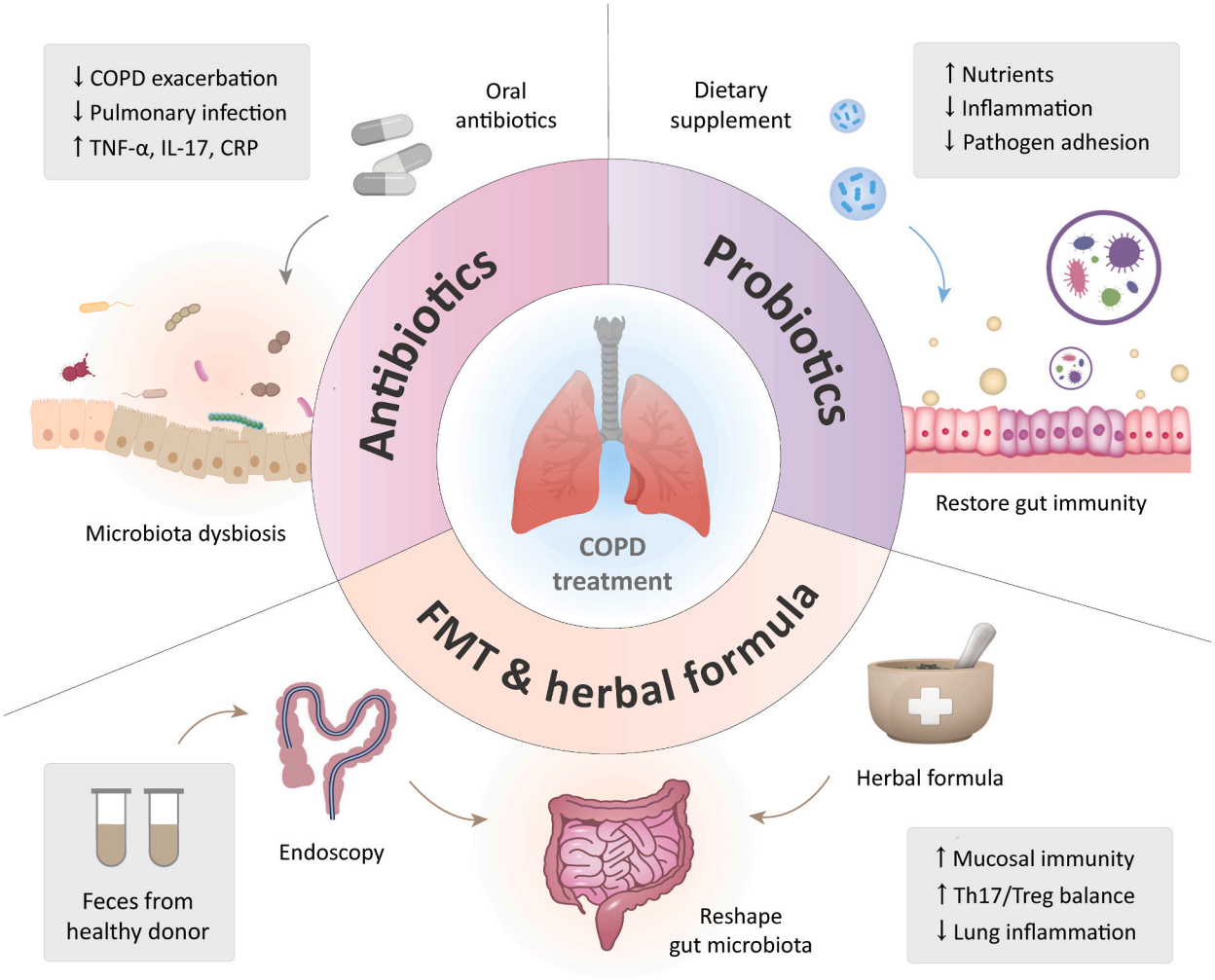

Fig. 2. Prospective treatments for COPD by modulating the gut-lung axis. The prospective COPD treatments include antibiotics, probiotics, FMT, and herbal formula. Conventional antibiotics therapy can reduce the risk of COPD exacerbation, but may induce gut microbiota dysbiosis and increase the level of inflammatory cytokines. Probiotics, as a dietary supplement, can prevent pathogen adhesion in the gut and restore intestinal immunity, and then modulate lung immunity in COPD. FMT and herbal formula can reshape gut microbiota through the gut-lung axis by enhancing mucosal immunity, correcting Th17/Treg balance in the gut, and reducing lung inflammation in COPD patients.

- Do the functions of gut microbiota and their metabolites listed in the tables of this review remain consistent across *in vitro*, in vivo, and patients' studies?
- Are there additional mechanisms or molecules involved in the mucosal immune response in the gut-lung axis?
- Do both the gut-lung axis and immune cell migration also impact the progression of other pulmonary diseases?
- How can the altered gut microbiota in COPD patients be leveraged in clinical research and applied to enhance current COPD treatments?

Consent for publication

All authors have checked the paper and made a final approval of the version to be published.

Data availability statement

The data associated with this study has not been deposited into a publicly available repository. The data included in this article is provided within the supplementary material and referenced throughout the article. We recognize the importance of sharing research data to facilitate evaluation, replication, and trust in scientific findings.

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CRediT authorship contribution statement

Zhi Song: Writing – review & editing, Validation, Supervision, Methodology, Data curation. **Yifei Meng:** Writing – original draft, Resources, Funding acquisition, Data curation, Conceptualization. **Michael Fricker:** Writing – review & editing, Validation, Resources, Formal analysis, Data curation. **Xin'ao Li:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Data curation. **Haochen Tian:** Writing – review & editing, Writing – original draft, Methodology, Funding acquisition, Data curation. **Yurong Tan:** Writing – review & editing, Validation, Resources, Methodology, Investigation. **Ling Qin:** Writing – review & editing, Writing – original draft, Validation, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30612.

References

[1] D. Adeloye, S. Chua, C.W. Lee, et al., Global and regional estimates of COPD prevalence: systematic review and meta-analysis, Journal of Global Health 5 (2) (2015) 186–202, https://doi.org/10.7189/jogh.05.020415.
[2] S. Gu, Y. Chen, Z. Wu, et al., Alterations of the gut microbiota in patients with coronavirus disease 2019 or H1N1 influenza, Clin. Infect. Dis. 71 (10) (2020) 2669–2678, https://doi.org/10.1093/cid/ciaa709.
[3] A.L. Raftery, E. Tsantikos, N.L. Harris, et al., Links between inflammatory bowel disease and chronic obstructive pulmonary disease, Front. Immunol. 11 (2020) 2144, https://doi.org/10.3389/fimmu.2020.02144 [published Online First: 20200911].
[4] M. Vutcovici, A. Bitton, P. Ernst, et al., Inflammatory bowel disease and risk of mortality in COPD, Eur. Respir. J. 47 (5) (2016) 1357–1364, https://doi.org/10.1183/13993003.01945-2015 [published Online First: 20160211].
[5] A. Ekbom, L. Brandt, F. Granath, et al., Increased risk of both ulcerative colitis and Crohn's disease in a population suffering from COPD, Lung 186 (3) (2008) 167–172, https://doi.org/10.1007/s00408-008-9080-z [published Online First: 20080311].

[6] N.D. Mutepe, R. Cockeran, H.C. Steel, et al., Effects of cigarette smoke condensate on pneumococcal biofilm formation and pneumolysin, Eur. Respir. J. 41 (2) (2013) 392–395, https://doi.org/10.1183/09031936.00213211 [published Online First: 20120627].

[7] L. Berkowitz, C. Pardo-Roa, G.A. Salazar, et al., Mucosal exposure to cigarette components induces intestinal inflammation and alters antimicrobial response in mice, Front. Immunol. 10 (2019) 2289, https://doi.org/10.3389/fimmu.2019.02289 [published Online First: 20190925].

[8] M. Fricker, B.J. Goggins, S. Mateer, et al., Chronic cigarette smoke exposure induces systemic hypoxia that drives intestinal dysfunction, JCI Insight 3 (3) (2018), https://doi.org/10.1172/jci.insight.94040 [published Online First: 20180208].

[9] D. Murphy, K. Bellis, D. Hutchinson, Occupational dust and cigarette smoke exposure might link rheumatoid arthritis to COPD, Lancet Respir. Med. 6 (8) (2018) e36, https://doi.org/10.1016/s2213-2600(18)30188-7 [published Online First: 20180511].

[10] K.F. Chung, I.M. Adcock, Multifaceted mechanisms in COPD: inflammation, immunity, and tissue repair and destruction, Eur. Respir. J. 31 (6) (2008) 1334–1356, https://doi.org/10.1183/09031936.00018908.

[11] L. Deng, J. Yan, H. Xu, et al., Prediction of exacerbation frequency of AECOPD based on next-generation sequencing and its relationship with imbalance of lung and gut microbiota: a protocol of a prospective cohort study, BMJ Open 11 (9) (2021) e047202, https://doi.org/10.1136/bmjopen-2020-047202 [published Online First: 20210902].

[12] Y.C. Chiu, S.W. Lee, C.W. Liu, et al., Comprehensive profiling of the gut microbiota in patients with chronic obstructive pulmonary disease of varying severity, PLoS One 16 (4) (2021) e0249944, https://doi.org/10.1371/journal.pone.0249944 [published Online First: 20210409].

[13] M. Brennan, M.J. McDonnell, M.J. Harrison, et al., Antimicrobial therapies for prevention of recurrent acute exacerbations of COPD (AECOPD): beyond the guidelines, Respir. Res. 23 (1) (2022) 58, https://doi.org/10.1186/s12931-022-01947-5 [published Online First: 20220314].

[14] K.G. Chan, K.T. Ng, Y.K. Pang, et al., Genome anatomy of Streptococcus parasanguinis strain C1A, isolated from a patient with acute exacerbation of chronic obstructive pulmonary disease, reveals unusual genomic features, Genome Announc. 3 (3) (2015), https://doi.org/10.1128/genomeA.00541-15 [published Online First: 20150528].

[15] J.L. Johnson, M.B. Jones, B.A. Cobb, Polysaccharide-experienced effector T cells induce IL-10 in FoxP3+ regulatory T cells to prevent pulmonary inflammation, Glycobiology 28 (1) (2018) 50–58, https://doi.org/10.1093/glycob/cwx093.

[16] W. Xiao, J. Su, X. Gao, et al., The microbiota-gut-brain axis participates in chronic cerebral hypoperfusion by disrupting the metabolism of short-chain fatty acids, Microbiome 10 (1) (2022) 62, https://doi.org/10.1186/s40168-022-01255-6 [published Online First: 20220417].

[17] P. Ghorbani, P. Santhakumar, Q. Hu, et al., Short-chain fatty acids affect cystic fibrosis airway inflammation and bacterial growth, Eur. Respir. J. 46 (4) (2015) 1033–1045, https://doi.org/10.1183/09031936.00143614 [published Online First: 20150528].

[18] M. Li, B. van Esch, G.T.M. Wagenaar, et al., Pro- and anti-inflammatory effects of short chain fatty acids on immune and endothelial cells, Eur. J. Pharmacol. 831 (2018) 52–59, https://doi.org/10.1016/j.ejphar.2018.05.003 [published Online First: 20180509].

[19] A.T. Dang, B.J. Marsland, Microbes, metabolites, and the gut-lung axis, Mucosal Immunol. 12 (4) (2019) 843–850, https://doi.org/10.1038/s41385-019-0160-6 [published Online First: 20190411].

[20] I. Zeller, M.V. Malovichko, H.E. Hurst, et al., Cigarette smoke reduces short chain fatty acid production by a Porphyromonas gingivalis clinical isolate, J. Periodontal. Res. 54 (5) (2019) 566–571, https://doi.org/10.1111/jre.12660 [published Online First: 20190414].

[21] L. Wang, Y. Cai, J. Garssen, et al., The bidirectional gut-lung Axis in COPD, Am. J. Respir. Crit. Care Med. (2023), https://doi.org/10.1164/rccm.202206-1066TR [published Online First: 20230308].

[22] K.L. Bowerman, S.F. Rehman, A. Vaughan, et al., Disease-associated gut microbiome and metabolome changes in patients with chronic obstructive pulmonary disease, Nat. Commun. 11 (1) (2020) 5886, https://doi.org/10.1038/s41467-020-19701-0 [published Online First: 20201118].

[23] S. Melo-Dias, M. Cabral, A. Furtado, et al., Responsiveness to pulmonary rehabilitation in COPD is associated with changes in microbiota, Respir. Res. 24 (1) (2023) 29, https://doi.org/10.1186/s12931-023-02339-z [published Online First: 20230125].

[24] J.C. Hogg, F. Chu, S. Utokaparch, et al., The nature of small-airway obstruction in chronic obstructive pulmonary disease, N. Engl. J. Med. 350 (26) (2004) 2645–2653, https://doi.org/10.1056/NEJMoa032158.

[25] M.M. Shikhagaie, Å.K. Björklund, J. Mjösberg, et al., Neuropilin-1 is expressed on lymphoid tissue residing LTi-like group 3 innate lymphoid cells and associated with ectopic lymphoid aggregates, Cell Rep. 18 (7) (2017) 1761–1773, https://doi.org/10.1016/j.celrep.2017.01.063.

[26] J.S. Silver, J. Kearley, A.M. Copenhaver, et al., Inflammatory triggers associated with exacerbations of COPD orchestrate plasticity of group 2 innate lymphoid cells in the lungs, Nat. Immunol. 17 (6) (2016) 626–635, https://doi.org/10.1038/ni.3443 [published Online First: 20160425].

[27] M. Zhao, F. Shao, D. Yu, et al., Maturation and specialization of group 2 innate lymphoid cells through the lung-gut axis, Nat. Commun. 13 (1) (2022) 7600, https://doi.org/10.1038/s41467-022-35347-6 [published Online First: 20221209].

[28] Q. Pu, P. Lin, P. Gao, et al., Gut microbiota regulate gut-lung Axis inflammatory responses by mediating ILC2 compartmental migration, J. Immunol. 207 (1) (2021) 257–267, https://doi.org/10.4049/jimmunol.2001304 [published Online First: 20210616].

[29] S. Chakradhar, A curious connection: teasing apart the link between gut microbes and lung disease, Nat Med 23 (4) (2017) 402–404, https://doi.org/10.1038/nm0417-402.

[30] J.L. Tweedle, G.S. Deepe Jr., Tumor necrosis factor alpha antagonism reveals a gut/lung Axis that amplifies regulatory T cells in a pulmonary fungal infection, Infect. Immun. 86 (6) (2018), https://doi.org/10.1128/iai.00109-18 [published Online First: 20180522].

[31] A.N. Kanj, T.J. Kottom, K.J. Schaefbauer, et al., Dysbiosis of the intestinal fungal microbiota increases lung resident group 2 innate lymphoid cells and is associated with enhanced asthma severity in mice and humans, Respir. Res. 24 (1) (2023) 144, https://doi.org/10.1186/s12931-023-02422-5 [published Online First: 20230531].

[32] N. Ottman, L. Ruokolainen, A. Suomalainen, et al., Soil exposure modifies the gut microbiota and supports immune tolerance in a mouse model, 1198-206.e12, J. Allergy Clin. Immunol. 143 (3) (2019), https://doi.org/10.1016/j.jaci.2018.06.024 [published Online First: 20180807].

[33] M.Y. Ramsheh, K. Haldar, A. Esteve-Codina, et al., Lung microbiome composition and bronchial epithelial gene expression in patients with COPD versus healthy individuals: a bacterial 16S rRNA gene sequencing and host transcriptomic analysis, Lancet Microbe 2 (7) (2021) e300–e310, https://doi.org/10.1016/s2666-5247(21)00035-5 [published Online First: 20210423].

[34] L. Zhao, S. Hu, M.L. Davila, et al., Coordinated co-migration of CCR10(+) antibody-producing B cells with helper T cells for colonic homeostatic regulation, Mucosal Immunol. 14 (2) (2021) 420–430, https://doi.org/10.1038/s41385-020-0333-3 [published Online First: 20200809].

[35] T.J. Schuijt, J.M. Lankelma, B.P. Scicluna, et al., The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia, Gut 65 (4) (2016) 575–583, https://doi.org/10.1136/gutjnl-2015-309728 [published Online First: 20151028].

[36] M. Aghapour, P. Raee, S.J. Moghaddam, et al., Airway epithelial barrier dysfunction in chronic obstructive pulmonary disease: role of cigarette smoke exposure, Am. J. Respir. Cell Mol. Biol. 58 (2) (2018) 157–169, https://doi.org/10.1165/rcmb.2017-0200TR.

[37] J.R. Turner, Intestinal mucosal barrier function in health and disease, Nat. Rev. Immunol. 9 (11) (2009) 799–809, https://doi.org/10.1038/nri2653.

[38] M. Moossavi, N. Parsamanesh, A. Bahrami, et al., Role of the NLRP3 inflammasome in cancer, Mol. Cancer 17 (1) (2018) 158, https://doi.org/10.1186/s12943-018-0900-3 [published Online First: 20181117].

[39] V. Woo, E.M. Eshleman, S. Hashimoto-Hill, et al., Commensal segmented filamentous bacteria-derived retinoic acid primes host defense to intestinal infection, 1744-56.e5, Cell Host Microbe 29 (12) (2021), https://doi.org/10.1016/j.chom.2021.09.010 [published Online First: 20211021].

[40] S. Gauguet, S. D'Ortona, K. Ahnger-Pier, et al., Intestinal microbiota of mice influences resistance to Staphylococcus aureus pneumonia, Infect. Immun. 83 (10) (2015) 4003–4014, https://doi.org/10.1128/iai.00037-15 [published Online First: 20150727].

[41] R.L. Brown, R.P. Sequeira, T.B. Clarke, The microbiota protects against respiratory infection via GM-CSF signaling, Nat. Commun. 8 (1) (2017) 1512, https://doi.org/10.1038/s41467-017-01803-x [published Online First: 20171115].

[42] Y. Yao, J. Zhou, X. Diao, et al., Association between tumor necrosis factor-α and chronic obstructive pulmonary disease: a systematic review and meta-analysis, Ther. Adv. Respir. Dis. 13 (2019) 1753466619866096, https://doi.org/10.1177/1753466619866096.

[43] Q. Wang, F. Li, B. Liang, et al., A metagenome-wide association study of gut microbiota in asthma in UK adults, BMC Microbiol. 18 (1) (2018) 114, https://doi.org/10.1186/s12866-018-1257-x [published Online First: 20180912].

[44] H. Wang, C. Lv, S. Wang, et al., NLRP3 inflammasome involves in the acute exacerbation of patients with chronic obstructive pulmonary disease, Inflammation 41 (4) (2018) 1321–1333, https://doi.org/10.1007/s10753-018-0780-0.
[45] K. Vermeersch, M. Gabrovska, J. Aumann, et al., Azithromycin during acute chronic obstructive pulmonary disease exacerbations requiring hospitalization (BACE). A multicenter, randomized, double-blind, placebo-controlled trial, Am. J. Respir. Crit. Care Med. 200 (7) (2019) 857–868, https://doi.org/10.1164/rccm.201901-0094OC.
[46] L. Nici, M.J. Mammen, E. Charbek, et al., Pharmacologic management of chronic obstructive pulmonary disease. An official American thoracic society clinical practice guideline, Am. J. Respir. Crit. Care Med. 201 (9) (2020) e56–e69, https://doi.org/10.1164/rccm.202003-0625ST.
[47] S. Salva, J. Villena, S. Alvarez, Immunomodulatory activity of Lactobacillus rhamnosus strains isolated from goat milk: impact on intestinal and respiratory infections, Int. J. Food Microbiol. 141 (1–2) (2010) 82–89, https://doi.org/10.1016/j.ijfoodmicro.2010.03.013 [published Online First: 20100318].
[48] L. Chunxi, L. Haiyue, L. Yanxia, et al., The gut microbiota and respiratory diseases: new evidence, J Immunol Res 2020 (2020) 2340670, https://doi.org/10.1155/2020/2340670 [published Online First: 20200731].
[49] Y. Panahi, M. Ghanei, E. Vahedi, et al., Efficacy of probiotic supplementation on quality of life and pulmonary symptoms due to sulfur mustard exposure: a randomized double-blind placebo-controlled trial, Drug Chem. Toxicol. 40 (1) (2017) 24–29, https://doi.org/10.3109/01480545.2016.1166250 [published Online First: 20160414].
[50] A. Karim, T. Muhammad, M. Shahid Iqbal, et al., A multistrain probiotic improves handgrip strength and functional capacity in patients with COPD: a randomized controlled trial, Arch. Gerontol. Geriatr. 102 (2022) 104721, https://doi.org/10.1016/j.archger.2022.104721 [published Online First: 20220510].
[51] R. Varraso, W.C. Willett, C.A. Camargo Jr., Prospective study of dietary fiber and risk of chronic obstructive pulmonary disease among US women and men, Am. J. Epidemiol. 171 (7) (2010) 776–784, https://doi.org/10.1093/aje/kwp455 [published Online First: 20100219].
[52] X. Qian, H.Y. Zhang, Q.L. Li, et al., Integrated microbiome, metabolome, and proteome analysis identifies a novel interplay among commensal bacteria, metabolites and candidate targets in non-small cell lung cancer, Clin. Transl. Med. 12 (6) (2022) e947, https://doi.org/10.1002/ctm2.947.
[53] H.C. Lai, T.L. Lin, T.W. Chen, et al., Gut microbiota modulates COPD pathogenesis: role of anti-inflammatory Parabacteroides goldsteinii lipopolysaccharide, Gut 71 (2) (2022) 309–321, https://doi.org/10.1136/gutjnl-2020-322599 [published Online First: 20210309].
[54] M. El-Salhy, J.G. Hatlebakk, O.H. Gilja, et al., Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study, Gut 69 (5) (2020) 859–867, https://doi.org/10.1136/gutjnl-2019-319630 [published Online First: 20191218].
[55] Y. Jia, T. He, D. Wu, et al., The treatment of Qibai Pingfei Capsule on chronic obstructive pulmonary disease may be mediated by Th17/Treg balance and gut-lung axis microbiota, J. Transl. Med. 20 (1) (2022) 281, https://doi.org/10.1186/s12967-022-03481-w [published Online First: 20220621].
[56] Y. Wang, N. Li, Q. Li, et al., Xuanbai Chengqi decoction ameliorates pulmonary inflammation via reshaping gut microbiota and rectifying Th17/treg imbalance in a murine model of chronic obstructive pulmonary disease, Int. J. Chronic Obstr. Pulm. Dis. 16 (2021) 3317–3335, https://doi.org/10.2147/copd.S337181 [published Online First: 20211207].
[57] J. Mao, Y. Li, Q. Bian, et al., The bufei jianpi formula improves mucosal immune function by remodeling gut microbiota through the SCFAs/GPR43/NLRP3 pathway in chronic obstructive pulmonary disease rats, Int. J. Chronic Obstr. Pulm. Dis. 17 (2022) 1285–1298, https://doi.org/10.2147/copd.S359428 [published Online First: 20220601].
[58] Y. Hu, Q. Shi, S. Ying, et al., Effects of compound Caoshi silkworm granules on stable COPD patients and their relationship with gut microbiota: a randomized controlled trial, Medicine (Baltim.) 99 (22) (2020) e20511, https://doi.org/10.1097/md.0000000000020511.