LITERATURE REVIEW

The Role of Gut Microbiota as a Trigger for Exacerbations in Pulmonary Obstruction Disorder in General

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ABSTRACT

Pulmonary diseases can be associated with the gastrointestinal (GI) system, particularly if an infection causes them. This relationship between organs is known as the gut-lung axis (GLA). Skin and mucosal surfaces are associated with microbiota (bacteria, fungi, viruses, macrophages, archaea, protists, helminths), which can trigger an immune response in GLA and serve a role in respiratory diseases. For instance, asthma can be inhibited by a specific antigen that is triggered by probiotics, the microorganisms found in the GI tract. Asthma incidence can be reduced by consuming fiber due to its ability to protect airways from infection. Pattern recognition receptors (PRRs) are the first immune component to identify microbial compounds in GI and lung epithelial cells. The PRRs then induce regulatory T-cell (T-reg) and Th-17 differentiation. Diet, antibiotics, and stress can all influence the structure and function of bacteria. This is known as dysbiosis. Lung microbiota can influence immune cell maturation and homeostasis. If the diversity of lung microbiota decreases, it will affect intestinal microbiota and may result in chronic respiratory disorders such as chronic obstructive pulmonary disease (COPD), asthma, and cystic fibrosis. This literature review explained how the interactions between the intestines and lungs can affect humans' health and well-being.

INTRODUCTION

Chronic pulmonary disorders, such as asthma bronchiale, chronic obstructive pulmonary disease (COPD), and cystic fibrosis, may manifest with gastrointestinal (GI) symptoms. For instance, GI symptoms are commonly accompanied by viral infections. This also suggests that the GI environment may contribute to the development of pulmonary disorders. The skin and the mucous membranes are host to a diverse ecology (microbiota) that includes bacteria, fungi, viruses, macrophages, archaea, protists, and helminths.[1] The significance of gut bacteriobiota in the community, as well as infectious illness, is presently being studied, although the long-term consequences are unknown.[2]

The microbiota of the upper and lower respiratory tracts is distinct, with more Firmicutes and Actinobacteria in the nostril and more Firmicutes, Proteobacteria, and Bacteroidetes in the oropharynx. In contrast, there are more Bacteroidetes and Firmicutes in the lung.[3,4] The composition and size of the lung microbiome change dynamically under the influences of different kinds of diseases. For instance, in patients with asthma and COPD, pathogenic Proteobacteria, especially Haemophilus, are increased, whereas in cystic

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fibrosis (CF) patients, *Candida albicans* are increased.[5–7] It follows that dysbiosis in the pulmonary microbiome, which imbalances its composition and size, affects disease occurrence, progression, and prognosis. Therefore, the lung microbiome can be considered an indicator of disease and diagnosis.[7]

The gut and respiratory microbiota exhibit compositional differences. The epithelia of both the GI and respiratory tracts develop from a common embryonic structure. The anatomical structures and functions of the two mucosal sites are similar, and early-life microbial colonization of the gut and lung exhibit similarities. Therefore, accumulating evidence has highlighted the relationship and crosstalk between the gut and lung, referred to as the gut-lung axis (GLA).[3,8] The gut microbiota is affected by many factors, such as drugs, diet, mode of delivery, and feeding practices, which may play a role in susceptibility to respiratory diseases.[9]

Inter-organ relationships, such as GLA, have not been as thoroughly investigated as the gut-brain axis. Mycobacterial involvement in human health and inter-organ relationships must be better understood.[10,11] Viruses are also recognized as important in several kinds of respiratory conditions and as collaborating with the human immune system. However, there is currently a scarcity of data on microbiota.[12] This literature review focused on the bacterial and fungal components of the microbiota and their interactions to produce an immune response in GLA, how the bacteriobiota and mycobiota of the lung and intestine can be linked to one another and subsequently induce the immune system, and their role in respiratory diseases.

GUT-LUNG AXIS

Although the gut and lung are physically different, they may be linked via complex anatomical pathways and the production of GLA by their microbiota. The lung microbiome has garnered a greater focus in the past few years than the intestinal microbiota.[11] Microbiota plays a crucial function in maintaining organ or tissue colonization homeostasis. Numerous studies, however, have shown that changes in the local microbiota can affect immunity in distant organs, most notably the link between the GI system and the pulmonary system.[13,14] According to additional studies, the intricate relationships involving gut microbiota and the immune system as a whole have impacted not just regionally but also various other organs or tissues.[8,15,16] Dysbiosis of the gut microbiota has been linked to the development and progression of chronic lung illnesses such as asthma.[8,15,16]

The balance of interactions between bacteria, nutrients, and host cells has physiological implications on metabolic processes, barriers, and trophic activities. Bacteria that infiltrate the GI mucosa and generate toxins cause infections.[17] Probiotics are beneficial microorganisms that influence the composition of the microbial community through direct immune cell effects or by manufacturing health-promoting metabolites. Salminen, *et al.* (2021) found that oral consumption of probiotics like *Lactobacillus rhamnosus*, *Bifidobacterium lactis*, *Bifidobacterium breve*, and *Mycobacterium veccae* suspension can induce antigen-specific T-cells that inhibit allergic responses.[18] *Enterococcus faecalis* FK-23 (LFK) can also inhibit allergic reactions by decreasing Th-17 responses. By enhancing the regulatory pathways of the immune system, some probiotics can be advantageous for asthma.[3]

Deacetylation activities, such as inducing T-reg, producing prostaglandin E2 (PGE2), and altering the anti-inflammatory function of dendritic cells, were discovered to prevent the development of allergic inflammation in the airway in mice that consumed dietary fiber and fermented products, which are part of short-fiber carbohydrates.[19] The same relationship was observed in humans, with alterations in gut microbiota resulting in a reduced incidence of asthma.[20,21] A study conducted on rodents fed a high-fat diet found that changes in the gut microbiome were inhibited, and airway allergic inflammation was increased.[9,16] Loss, *et al.*, as cited by Wypych, *et al.* (2019), found that drinking unpasteurized milk in the first year of life can prevent airway infections.[22] Variations in the composition of the GI and airway microbiota have been associated with chronic pulmonary diseases and respiratory infections. Changes between these two compartments, such as overlap, or other variables, such as food, may impact the microbiota of the intestines and airways.[22,23] Figure 1 also depicts the link between the stomach and the lungs. A study of microorganisms in the lower airway and buccal cavity of nonsmokers and smokers helped to identify a healthy microbiome in the lower respiratory tract. Streptococcus, Prevotella, and Veillonella were the most common species in lung colonization, as they were in the oral cavity.[10,11]

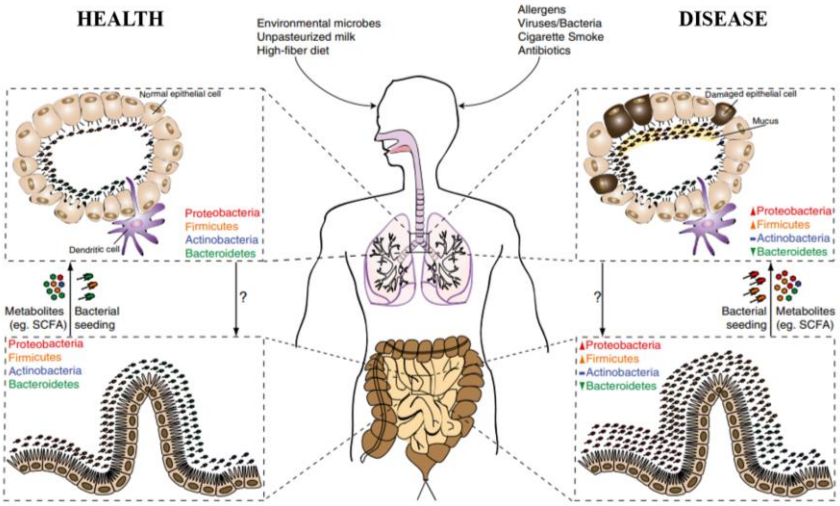

Figure 1. Intestinal-pulmonary transmission in both normal and abnormal airways. Villi (Bacteroides and Firmicutes) comprise the majority of the GI and airway microbiota. Both Proteobacteria and Firmicutes can arise as a consequence of dysbiosis in both microbiota. The GI microbiota influence the composition of the airway microbiota and the immune response through the direct spread of bacteria in the airway and the spread of bacterial metabolites, such as short-chain carbohydrates that can stimulate bacterial growth.[10,11]

ORIGIN AND COMPOSITION OF LUNG MICROBIOTA

A newborn lung microbiome investigation revealed a comparison of gut and lung microbiota. Because normal microbiological cultures from healthy persons are unable to produce lung bacteria, the lower respiratory tract is deemed sterile. However, developments in sequencing tools that may find microbial deoxyribonucleic acid (DNA) in stable lungs are putting this orthodoxy into question. Historically, traditional culture-based research and classical teaching have shown that the typical lung is bacteria-free, and this belief prevails in modern medicine.[22] The gut and the lung have a distinct link that is critical for maintaining homeostasis and the host's immune system.[24]

THE ROLE OF MICROBIOTA AS MAINTENANCE IN LUNG HOMEOSTASIS

To maintain homeostasis in the GI tract, the pattern recognition receptors (PRRs) recognize microbial chemicals and trigger the development of regulatory T-cells (T-reg) and Th-17 cells. The presence of PRRs in the lung microbial chemicals from the lung microbiome was previously identified and turned naïve T-cells into Th-1 cells but not Th-2 cells. Th-2 cells dominate the immunological system before t delivery. After birth, the polarization of naïve T-cells in the lung will shift from Th-2 to Th-1, protecting babies from asthma and allergic disorders. In another study involving mice, the frequency of Th-2-specific germinal and pathogen-free phenotypic immune responses increased, as did vulnerability to house dust mite-induced allergic asthma.[14,25] Through the mucosa, exposure to bacteria or other components like lipopeptides, peptidoglycans, lipopolysaccharides (LPS), or DNA, can induce Th-1 immune responses and protect mice from asthma and allergies.[25]

INTERACTIONS BETWEEN GUT AND LUNGS

The epithelial surfaces of the GI tract and the respiratory system are susceptible to an extensive spectrum of bacteria. Consumed organisms can access these two areas, and microbiota from the GI tract can enter the lungs via aspiration. Both the intestine and respiratory mucosa contain microbial invasion barriers, and proper microbiota colonization offers disease resistance, such as through the creation of bacteriocin.[26] Furthermore, inoculating rapidly evolving companion microbes in the gut, such as *Segmented Filamentous Bacteria* (SFB), *Bifidobacterium spp*., and the colonic species *Bacteroides*, increases the production of antimicrobial peptides, secretory immunoglobulin A (sIgA), and pro-inflammatory cytokines.[21,26]

Antibody system development needs signals from the microbiome, including microbial components and metabolites.[21] Environmental variables such as nutrition, antibiotic therapy, and stress can affect the gut microbiota of people, resulting in a decrease in helpful bacterial species and an increase in pathogenic bacterial species. Dysbiosis, or disturbance in microbial composition and activity, can affect tissue and immunological homeostasis and is linked to a number of inflammatory disorders both inside and beyond the GI tract.[27] Despite the preponderance of data implying that there is cross-talk between the intestines and lungs, a link in the other direction is still possible. Chronic pulmonary diseases such as asthma, COPD, and cystic fibrosis have dysbiotic airway microbiota as well as features of GI illnesses such as irritable bowel syndrome

(IBS). Furthermore, pulmonary influenza infection in rats can decrease gut immunity and change gut microbiota. The ensuing dysbiosis in the colon increases inflammation by increasing the number of Enterobacteriaceae and reducing the number of *Lactobacilli* and *Lactococci*.[28] In general, it seems that there is a strong interdependence between the gut and the lung, which is critical for maintaining homeostasis and the host's immune system.[24]

In recent years, the importance of the respiratory microbiome in lung immune development and homeostasis has been recognized.[22] Colonization of the respiratory tract is a crucial indicator for the maturation of local immune cells. Preclinical research has confirmed the relationship between airway microbial colonization, regulation, and maturation of airway immune cells.[25] Mice lacking bacteria produce more IgE and cytokines associated with Th-2, which promotes allergic airway inflammation.[29] In early life, exposure to commensal bacteria reliably reduces Th-2-related cytokine production during allergen testing and activates regulatory T-cells. Local antigens of the lung microbiota, including protection against influenza and other viruses, are also required for the development of memory B-cells in the lung. The connection between the lung microbiota and immunology is also bidirectional. Considerable lung inflammation may modify the makeup of the lung microbiota, as seen in Figure 2.[11,29]

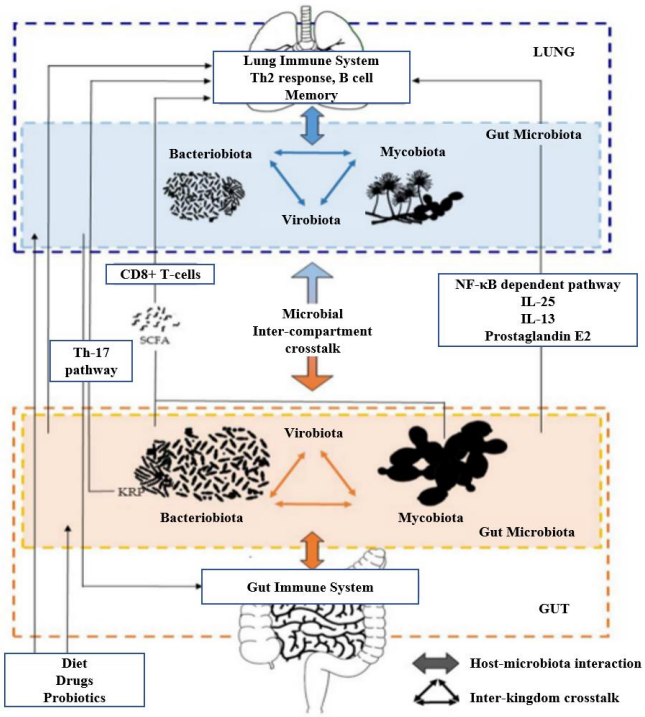

Figure 2. Microbial interactions, interactions between compartments, environment, diet, and GLA[11,29]

GUT-LUNG AXIS IN RESPIRATORY DISEASE

There is currently a scarcity of data on acute infectious illnesses linked with influenza infection, as well as the influence of gut and lung microbiota. Antibiotic therapy, on the other hand, can significantly diminish mice's immunological response to the influenza virus. Mice given a high-fat diet and infected with influenza, on the other hand, outlived infected controls due to an increase in Ly6c monocyte production. These monocytes enhance macrophage numbers while having a limited ability to create CXCL-1 locally, decreasing neutrophil recruitment in the airways and tissue damage. Short-chain carbohydrates, on the other hand, improved the effector activity of $CD8^+$ T-cells in rats fed a high-fat diet.[14] The microbiota of the lungs and the intestines are essential for preventing bacterial pneumonia. By boosting granulocyte-macrophage colony-stimulating factor (GM-CSF) synthesis in the lung via IL-17 and Nod2 stimulation, the lung microbiota can protect against *Streptococcus pneumoniae* and *Klebsiella pneumoniae* respiratory infection.[30] The gut microbiota also significantly influences pulmonary bacterial infection responses. In mice devoid of bacteria, mortality and morbidity increased during acute pulmonary infections with *K. pneumoniae*, *S. pneumoniae*, or *P. aeruginosa*.[30]

A mouse model of pulmonary infection had poorer outcomes when treated with a broad-spectrum antibiotic that disrupted the gut microbiota of rodents. Alveolar macrophages from rodents with a reduced gut microbiota due to antibiotic treatment were mechanistically less responsive to stimulation and had diminished phagocytic capacity. Toll-like receptor (TLR) agonist priming of antibiotic-treated animals

restored resistance to pulmonary infection.[31] SFB appears to be a key gut microbiota component for pulmonary defense against bacterial infection due to its potential to induce the production of Th-17 cytokines and IL-22 and to boost neutrophil counts in the lung during *Staphylococcus aureus*-caused pneumonia. Chronic infection disease modulation will also hinge on the microbiota in the gut and lungs. For instance, there is a correlation between the severity of *Mycobacterium tuberculosis* infection and the intestinal microbiota.[30] Numerous studies have examined the effect of GI and lung microbiota on chronic respiratory diseases like COPD, asthma, and cystic fibrosis.[32] COPD severity and exacerbations were associated with a decline in lung microbiota diversity and an expansion of *Proteobacteria*.[28]

It seems that individuals with hereditary mannose-binding lectin impairment have a more diversified pulmonary microbiome and are less likely to have exacerbations, which shows not merely a correlation but also a causative association. In addition to the normal flora of the lungs, as seen by increased GI permeability in COPD exacerbation-treated patients, the gut microbiota is also involved in COPD exacerbations. Regardless of the source of permeability (hypoxia or proinflammatory status), trimethylamine-N-oxide levels in the gut microbiome have been associated with mortality in COPD patients.[30] Comorbidities and age can explain this association, but its impact is uncertain. More studies are needed to examine the function of GLA in COPD and identify causal linkages. Early-life disruptions in gut fungal and bacterial colonization, such as decreased gut microbial diversity following neonatal antibiotic use, are critical for generating childhood asthma.[8]

Gastroesophageal reflux disease (GERD) is one of the most common comorbidities of COPD. It is associated with exacerbations in patients with COPD in a national cross-sectional cohort study that included data from 141,057 patients with COPD using the Korean National Health Insurance Database.[33] Cigarette smoking is a risk factor for both GERD and COPD in the general population.[34] Nicotine may affect oesophageal sphincter tone and clearance and induce relaxation of the oesophageal sphincter muscle, possibly increasing the duration of acid exposure and frequency of reflux events. The rate of COPD exacerbations is twice as high in patients with GERD symptoms as in those without GERD symptoms.[32] A potential pathogenic mechanism for these COPD exacerbations might be related to the microaspiration of gastric contents and/or vagal irritation from gastroesophageal reflux, which may constitute airway irritants.[32,34] IL-8 upregulation in bronchial biopsy samples from patients with COPD is associated with severe exacerbations and increased neutrophil recruitment.[35]

COPD and periodontitis share common risk factors, including cigarette smoking. A review by Wang, *et al*. (2023) explained that periodontal treatment in patients with COPD improved lung function and decreased the frequency of COPD exacerbations.[34] It is assumed that a disruption in the composition of the oral microbiota after periodontal treatment may play a role in the remission of COPD exacerbations.[34,36] It can be hypothesized that excessive proinflammatory mediators produced in the lungs of patients with COPD affect the intestine through systemic circulation, contributing to intestinal disease. Correspondingly, continuous intestinal inflammation can also exacerbate lung diseases by the presence of inflammatory mediators in the systemic circulation. During inflammation, the gut-associated lymphoid tissue regulates lymphocyte trafficking from intestinal tissue through the systemic circulation, which reflects the bronchus-associated lymphoid tissue, and these lymphocytes from the intestine and the lungs migrate to other mucosal sites as part of their shared mucosal immune system.[35] Moreover, inflammatory mediators, such as circulating TNF-a, have been strongly implicated in comorbidities associated with COPD and have been implicated in the pathogenesis of both COPD and inflammatory bowel disease (IBD).[34,37]

These microbial disturbances are linked to changes in fecal short-chain fatty acid (SCFA) concentrations. Murine models were used to assess causation and inoculation with bacteria not seen in asthmatic patients' microbiome reduced airway inflammation.[8,30] In addition, *Bacteroides fragilis* appears to be involved in immunological homeostasis, adjusting the host's systemic Th-1/Th-2 ratio and guarding against allergen-induced respiratory diseases.[8,38] Nevertheless, this remains unclear since some studies have suggested that early Bacteroides colonization, especially *B. fragilis*, might be a precursor to asthma.[39] In the absence of pulmonary fungal expansion, intestinal fungal proliferation (after antibiotic treatment or intestinal colonization procedures with *Candida* or *Wallemia mellicola*) increases the prevalence of asthma via IL-13.[40] *Candida's* production of PGE2 in the intestines can travel to the lungs, where it promotes pulmonary macrophage polarization and allergic airway inflammation.[41] *W. mellicola* overestimation in the gut, which has been linked to various gut microbiome illnesses, appears to have long-term impacts on pulmonary immune responses and asthma severity in mice. These effects are mediated by Th2 pathways, specifically IL-13 and, to a lesser extent, IL-17, as well as goblet cell differentiation, fibroblast

activation, and B cell IgE production. These findings suggest that GLA, particularly via the intestinal microbiota, serves a significant role in asthma.[40]

Currently, the mechanisms of probiotic regulation of lung health and disease have become a research hotspot since there is increasing evidence that probiotics have protective and therapeutic effects on respiratory diseases by optimizing microbial balance in the GI tract.[42] Another study indicated that probiotic intervention for pregnant women and their infants who were at a high risk of allergy could protect cesarean-delivered children from allergic disease.[9,39] Additionally, a double-blind, randomized, placebo-controlled trial of 160 asthmatic children suggested that *Lactobacillus* can reduce asthma severity and improve asthma control.[39]

In recent years, numerous randomized controlled trials (RCTs) have shown that restoration of the gut microbiota followed by probiotic supplementation is related to the improvement of CF, further strengthening the idea that the gut microbiota can influence airway inflammation in CF. *Lactobacillus* administration caused a reduction in bacterial density and an increase in microbial diversity in the gut, as well as had beneficial effects on exacerbation risk and quality of life in CF patients.[3,43] However, some inconsistent results were also yielded. For example, Biervliet, *et al*. (2018) found no significant differences in pulmonary function and disease exacerbations between probiotic and placebo groups.[43] Therefore, according to a meta-analysis, fastidiously designed and adequate RCTs are needed to assess the safety and efficacy of probiotics and to ascertain the specific probiotic strains or doses that can be of significant benefit to CF patients.[44]

Similarly, there have been relatively few studies about probiotics that revealed the connection between the gut microbiota and COPD. For example, intragastric supplementation with *Lactobacillus rhamnosus* and *Bifidobacterium breve* in mice with COPD attenuated airway inflammation and alveolar damage. In vitro, these two probiotics showed a similar anti-inflammatory effect on cigarette smoke-induced inflammation in human macrophages. In the future, additional studies conducted on COPD patients are required to investigate and confirm the role of probiotics in COPD and to provide new therapeutic strategies for COPD.[3,45]

Probiotic administration may be an effective strategy to maintain or restore a functional microbiome, such as the use of probiotics to prevent allergic asthma. Several studies have examined the role of oral probiotics in the prevention of upper respiratory tract (URT) infections, with the majority (17 of 21) providing evidence of their beneficial effects.[12,46] In vitro studies on cigarette smoke-induced diseases, such as COPD, demonstrated that the administration of *Lactobacillus rhamnosus* and *Bifidobacterium breve* eliminated the release of proinflammatory mediators from macrophages in response to cigarette smoke.[46–48]

SUMMARY

GLA is now recognized as a distinct pathway involving bidirectional microbial and immunological interactions between the gut and the lungs. Dysbiosis of the lung microbiota has been linked to chronic lung disorders. However, it is unclear if dysbiosis is a result of immunological dysregulation and disease development or progression. In the future, healthy lung microbiota communities could be established to advance the understanding of the lung microbiota's complexity, as well as its genetic and metabolic potential, and even manipulate the lung microbiota as a potential therapeutic method for treating chronic lung diseases.

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Conflict of Interest

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Authors' Contributions

Idea and concept: DW, ETMS. Design and manuscript writing: DW, ETMS, YJPP, AP. Data collection and processing: ETMS, YJPP, AP. Control and supervision: DW, SS, DA. Review and revision: DW, SS, DA. All authors contributed and approved the final version of the manuscript.

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