Literature Review

Gut-Lung Axis

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Abstract

Microbiota and the body's immune system have a two-way interaction that is interconnected. The microbiota plays a role in the formation and maturation of the immune system, on the other hand, the immune system shapes the composition and function of the microbiota. This interaction is important in maintaining the body's immune system's homeostasis. The human intestine contains various types of microbes that form the gut microbiota. Various studies have found that changes in the gut microbiota are associated with immunity in distal tissues such as the lung. This gives rise to the concept of a feedback relationship between the gut and lung organs called the gut-lung axis. Through this axis, changes in the composition of the gut microbiota not only cause abnormalities in the gut but also affect microbiota in the lungs and can cause disease. One of the important routes in the transmission of substances from the intestine is through the mesenteric lymphatics. Probiotics can help improve the gut's defense mechanism. A high-fiber diet can also reduce pathogenic bacteria by increasing levels of short-chain fatty acids. Therefore, a healthy lifestyle is needed to maintain the balance of the microbiota.

Keywords: gut-lung axis, immunity, microbiota

INTRODUCTION

Human organs consist of a collection of tissues that work together. The tissue contains microbes, including bacteria, viruses, fungi, and parasites that live in host cells to form a microbiota. The microbiota plays a role in the formation and maturation of the immune system. Meanwhile, the immune system forms the composition and function of the microbiota that affect the inflammatory response in the body. This interaction is essential in maintaining the homeostasis of the human immune system.[1,2] Microbes also have a mutualistic relationship with the host cell. Microbes benefit from a nutrient-rich environment, whereas microbes have a vital role in the fermentation of food components to produce nutrients, vitamins, and metabolites.[2,3]

The human gut contains more than 10^{14} cells with various bacteria that make up the gut microbiota.[3,4] Changes in the composition and function of the microbiota are called dysbiosis.[1–5] Dysbiosis can be influenced by various factors such as genetic or exogenous factors such as diet, use of antibiotics, and exposure to cigarette smoke. These conditions are associated with a decline of immune

responses that occurs in the gastrointestinal tract and other organs, including the respiratory tract.[2–6]

Alterations in the gut microbiota are associated with changes in lung immunity. On the other hand, the microbiota in the lungs also influences the microbiota in the gut. It gives rise to the concept of a feedback relationship between the gut and lung organs called the gut-lung axis. Through this axis, disease in the intestine can cause pathological lung conditions and vice versa.[1–6] This literature review aims to provide knowledge about the relationship between the intestine and the lungs through the gut-lung axis which can be useful in the management of lung disease.

GUT MICROBIOTA

Many studies have been conducted on microbes in the gastrointestinal tract, especially in the intestines. The microbiota varied along the gastrointestinal tract. Environmental pH, bile acid concentration, digestive retention time, and host defense factors influence these differences.[5]

The gastrointestinal tract is dominated by four bacterial phyla, namely *Firmicutes* (e.g., *Lactobacillus, Bacillus, Clostridium*), *Bacteroidetes* (e.g., *Bacteroides*), *Proteobacteria* (e.g., *Escherichia*) and *Actinobacteria* (e.g., *Bifidobacterium*). Some other types with fewer numbers are *Fusobacteria*, *Verrucomicrobia*, and *Spirochaeta*.[5] The number of T cells in the gut, such as CD4+ and T helper (Th) cells, including Th1, Th2, and Th17, is influenced by the microbiota in the intestinal epithelium. The gut microbiota can induce regulatory T cells (Treg) in the large intestine that regulate the immune response by increasing the production of transforming growth factor (TGF)-β.[1]

Gram-positive bacteria can translocate through dysfunctional mucus layers as in ulcerative colitis and induce an immune response. Commensal bacteria such as *Segmented filamentous bacteria* (SFB) induce the accumulation of Th17 cells in the small intestine.[5,7]

The microbiota furthermore plays a role in inducing antibody responses. Production of immunoglobulin A (IgA) occurs through the gut-associated lymphoid tissue (GALT). Through effector sites on these cells, plasma cells produce specific antibodies and form mucosal immunity. This circumstance indicates a relationship between gut microbiota and intestinal mucosal immunity.[1,2]

GUT BARRIER AND BLOOD VESSEL

The gut barrier plays a vital role in metabolic homeostasis. They regulate the absorption of water, electrolytes, and nutrients and also obstruct bacteria or harmful substances in the intestines from entering circulation. The intestinal barrier consists of three layers, namely mucus, epithelium, and endothelium, as shown in Figure 1. The mucus layer lining the lumen is a fibrous tissue comprised of protein and mucin produced by goblet cells. This layer also contains antimicrobial peptides secreted by Paneth cells and

immunoglobulin A secreted by plasma cells.[8]

The small intestine has a layer of connective tissue and mucus, while the large intestine has two layers of mucus. The epithelial layer is formed by enterocytes, goblet cells, Paneth cells, and other enteroendocrine cells, which are connected through tight junctions (TJ), adherent junctions (AJ), desmosomes, and gap junctions. Disruption of the intestinal barrier is common in critically ill patients. Adequate enteral therapy is essential in maintaining the intestinal defense system and reducing the incidence of multiorgan failure in septic and trauma patients. Inflammatory mediators such as Interferon Gamma (IFN-ɣ), Interleukin-6 (IL-6), and Tumor Necrosis Factor Alpha (TNF-α) can disrupt the TJ and increase epithelial permeability.[1,8]

In response to stress, the blood vessels in the intestines will experience vasoconstriction to maintain the blood supply to vital organs. This condition will affect the protuberances in the intestines, which are drained by an artery and are sensitive to damage. A brief ischemic period can cause local tissue damage, epithelial apoptosis, and intestinal barrier breakdown. The damaged barrier layer will become a site to spread bacteria, toxins, and other tissue products in the intestine through the barrier.[1,8]

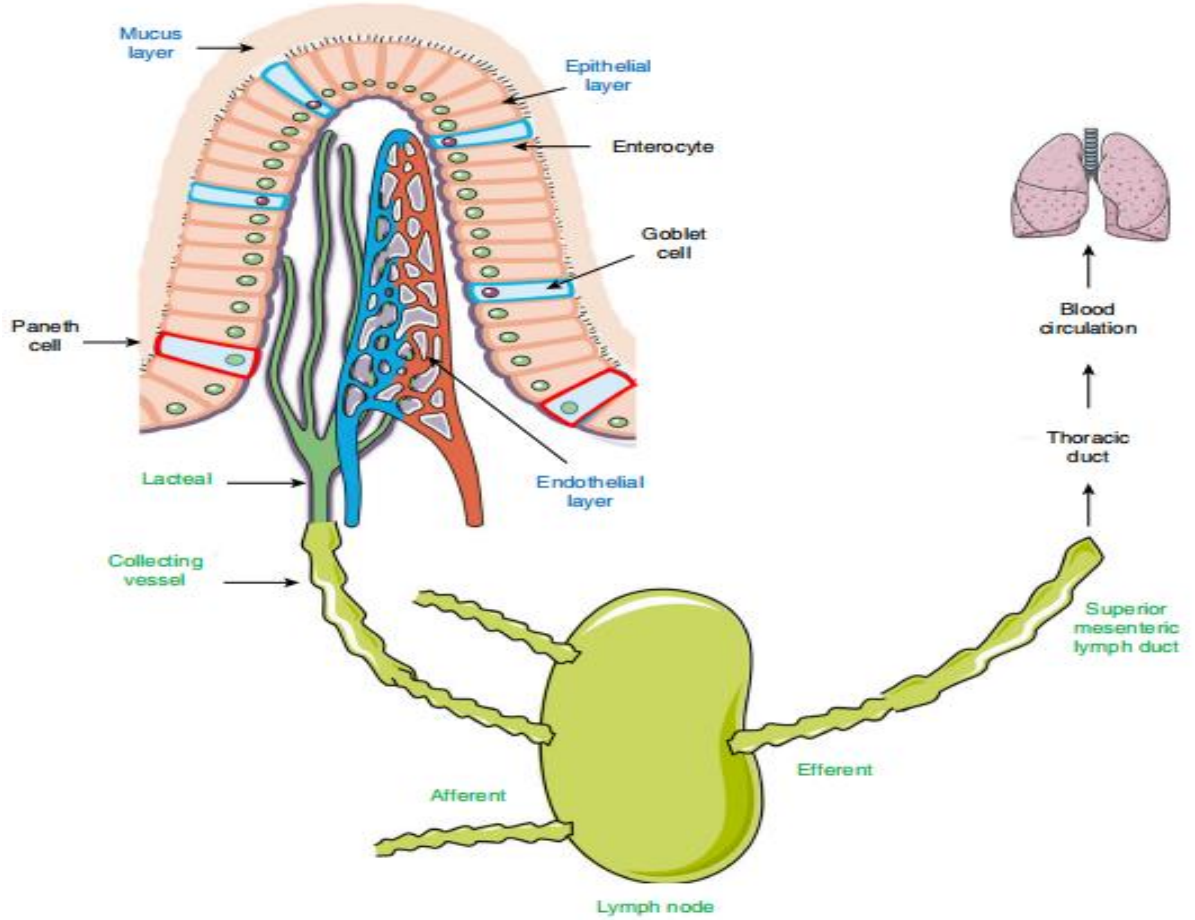
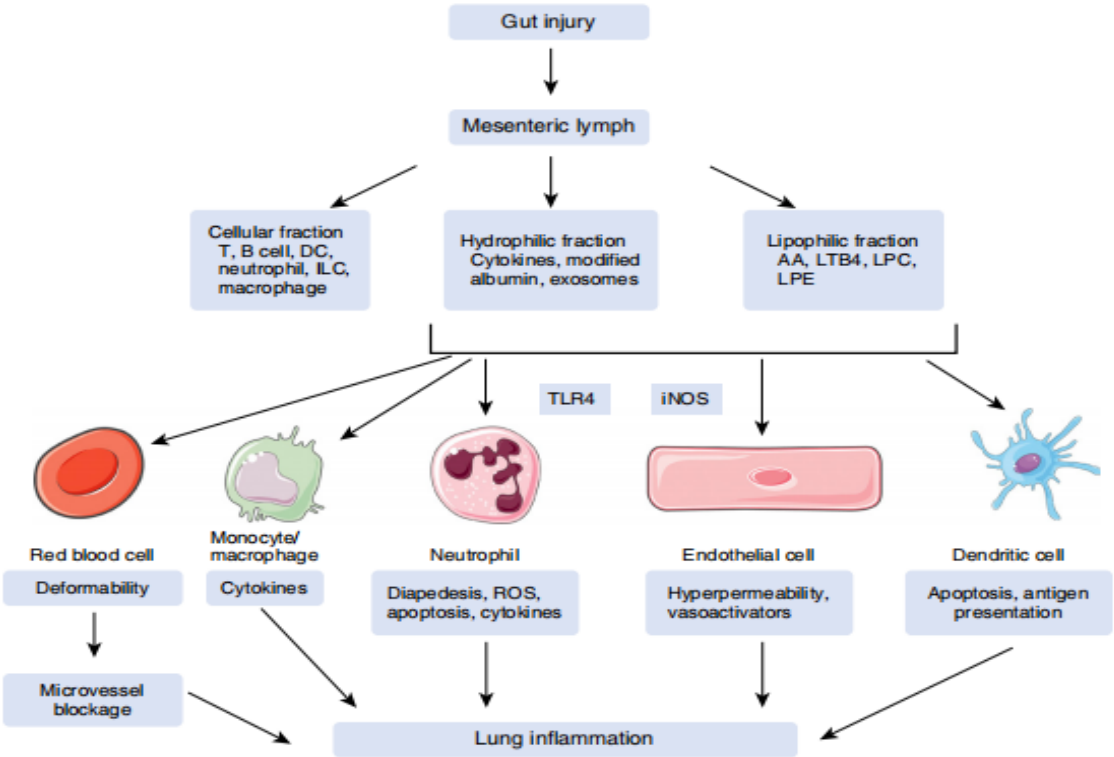


Figure 1. Intestinal barrier and lymphatic system[8]

MESENTERIC LYMPHATICS

The intestine has two drainage systems: the portal venous system and the mesenteric lymphatic system. Mesenteric lymphatic vessels are arranged to form a network called lacteals. Interstitial fluid exits the intestine into the lacteals to form lymph fluid. The fluid travels through the lymphatic vessels to the superior mesenteric lymphatic duct, the thoracic duct, or returns to the blood circulation via the subclavian vein. Under pathological conditions, neutrophils traveling to inflamed tissues may migrate to lymph nodes. Dendritic cells also exit the lamina propria into the spleen in the small intestine.[1,7,8]

In conditions of intraperitoneal infection, neutrophil levels increase in the mesenteric lymphatics and form systemic inflammation that can cause pulmonary disorders. Based on these circumstances, several studies have stated that mesenteric lymphatics are essential for spreading substances from the intestines to other organs, including the lungs. After the damage to intestinal tissue, mesenteric lymphatics lipophilic and hydrophilic components can activate endothelial cells, neutrophils, and monocytes or macrophages, as shown in Figure 2. These components induce endothelial cell barrier dysfunction, slow neutrophil apoptosis, and inhibit red blood cell deformability and dendritic cell function. These will contribute to systemic inflammation and acute lung tissue damage.[1,7,8]



Note: AA = arachidonic acid; ILC = innate lymphoid cell; iNOS = inducible nitric oxide synthase; LPC = lysophosphatidyl-choline; LPE = lysophosphatidyl-ethanolamine; LTB4 = leukotriene B4; ROS = reactive oxygen species; TLR4 = Toll-like receptor 4

Figure 2. Mechanism lung inflammation after gut injury via mesenteric lymphatic[8]

LUNG MICROBIOTA

Previous studies on lung microbiota state that normal lungs are in sterile conditions, free from microbes.[1,3–7] The Next Generation Sequencing (NGS) technique was developed with the development of science and technology. Through amplification and analysis of 16S ribosomal RNA (rRNA), there were microbes in the lungs of healthy people that formed the microbiota like in the intestines.[2,9]

The phyla in healthy people's lungs include *Bacteroidetes, Proteobacteria, Firmicutes, Actinobacteria, Fusobacteria*, and *Cyanobacteria*. The most dominant phyla are *Bacteroidetes, Firmicutes*, and *Proteobacteria*. Some dominant types of bacteria are *Pseudomonas, Streptococcus, Prevotella*, *Fusobacteria*, and *Veillonella.*[3,9]

The benefits of the lung microbiota for host cells include enhancing the function and structure of the mucosa, forming the adaptive and innate immune systems, and protecting against harmful pathogenic infections. Before birth, the body's immune system pattern is dominated by Th2 cells. After birth, pattern recognition receptors (PRR) will induce changes in Th2 to Th1, protecting against asthma and allergies in neonates. Research in mice with the administration of bacteria or their components such as lipopeptides, peptidoglycans, and lipopolysaccharides (LPS) can induce Th1 immune responses against asthma and allergies, as shown in Figure 3.[10]

In the lungs, the number of bacteria increases in the first two weeks after birth. The bacterial phylum changed from *Gammaproteobacteria* and *Firmicutes* to *Bacteroidetes*. Changes in the microbiota are related to the formation of T_{reg} cells in the lungs, reducing the incidence of allergies.[10]

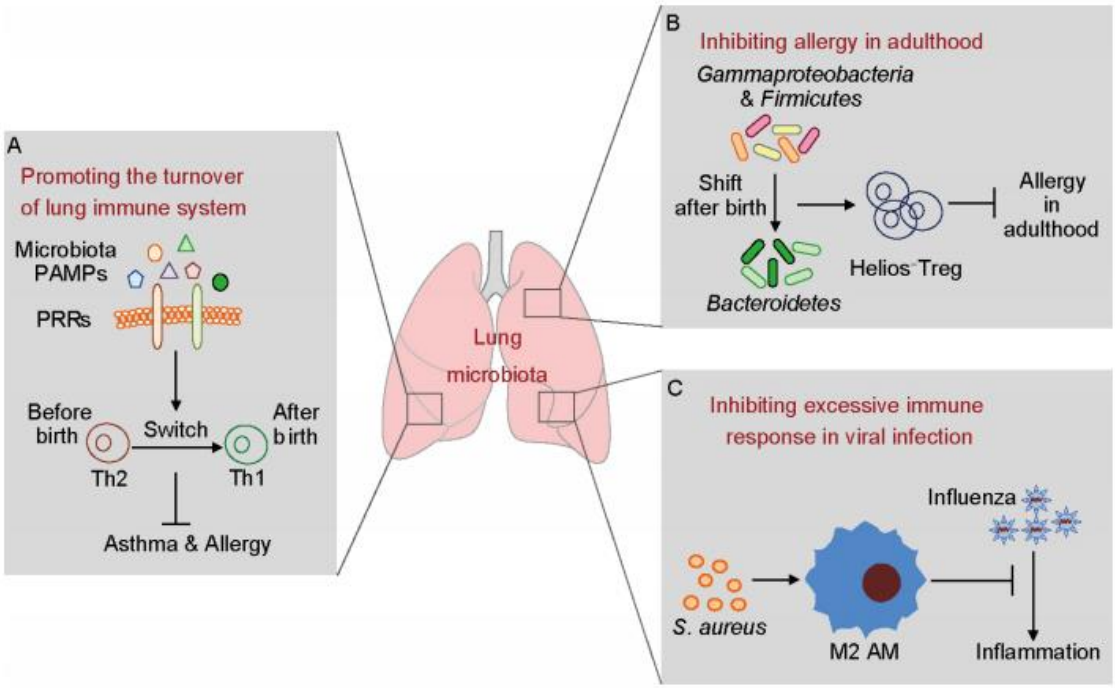


Figure 3. The function of lung microbiota in immune system[10]

Previous studies found that the microbiota in the upper respiratory tract also protects against inflammation in the lungs caused by influenza infection. *Staphylococcus aureus* colonizes the upper respiratory tract in humans increasing M2 macrophage differentiation, which significantly reduces the inflammatory response in the lung.[10]

MICROBIOTAS IN LUNG DISEASE

Asthma is a chronic and multifactorial disease caused by genetics and environmental factors such as air pollution and allergens. In asthmatic patients, *Proteobacteria* were found more, and *Bacteroidetes* were less. Research by Ege found that children who grew up in rural areas were exposed to more environmental microbes and had a lower risk of developing asthma than children who lived in cities.[10,11] Changes in the microbiota were also found in patients with severe COPD. Under these conditions, more *Proteobacteria* or *Firmicutes* were found, and *Bacteroidetes* were less, similar to asthmatic patients.[1,3]

In tuberculosis (TB), chronic infection can be latent for several years before reactivation and destroying lung tissue. Research conducted on TB patients while the patient was infected and while taking anti-tuberculosis drugs (ATD) showed that the composition of the bacteria in the gut changed and was associated with disease progression. ATD therapy can alter the gut microbiota causing a dysbiosis condition that occurs even after discontinued therapy. Long-term ATD therapy can increase the patient's susceptibility to other diseases.[6]

Research conducted by Diallo et al showed that there were changes in the gut microbiota and impaired innate immunity in patients receiving ATD therapy through decreased expression of major histocompatibility complex class II (MHC-II) and CD86. It would decrease the ability of antigen presentation and activation of dendritic cells in the lung.[6]

Other studies have also shown a decrease in the function and activity of alveolar macrophages that influence by metabolites produced by gut microbiota. The balance of gut microbiota composition plays an important role in maintaining the response of alveolar macrophages against infection.[6]

Microbiota studies in bronchiectasis patients found that *Haemophilus*, *Streptococcus*, and *Pseudomonas* were associated with the infection. Woo's study consisted of twenty-nine bronchiectasis patients who were followed for 16 years. The microbiota found were dominated by *Pseudomonas* and *Haemophilus*. The Bronchiectasis and Low-dose Erythromycin Study (BLESS) showed that *Haemophilus*-dominated patients had fewer exacerbations than *Pseudomonas*-dominated patients. Patients with *P.aeruginosa* infection had a worse outcome, more frequent exacerbations, decreased lung function, more sputum production, and a greater need for antibiotic therapy.[12–14]

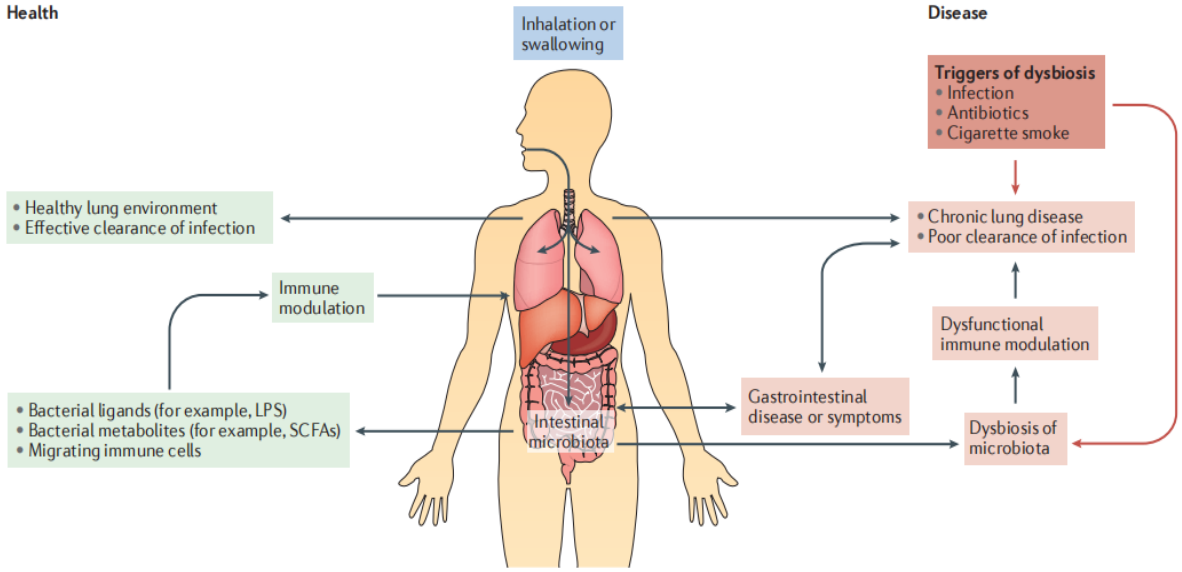


Figure 4. Interaction of immune system and intestinal microbiota in health and disease[5]

GUT-LUNG AXIS

The microbiota plays a vital role in tissue homeostasis. The complex interactions between the gut microbiota and the host immune system have crucial local effects on the gut and other tissues and organs such as the lung. Symptoms in the respiratory and gastrointestinal tract often coexist and lead to overlapping pathologies. This gives rise to a concept of the relationship between the intestines and the lungs called the gut-lung axis. Through this axis, changes in the composition of the gut microbiota not only cause abnormalities in the gut but also affect other organs in the respiratory system and cause disease.[1,2,11,15,16,3–10]

Research in rats has shown that the reduced bacterial microbiota in the gut caused by antibiotics can increase viral infections in the lungs. Another study in humans found differences in gut microbiota in COPD patients compared to healthy controls through fecal examination.[3,10]

Intestinal microbiota dysbiosis is associated with the pathogenesis and course of chronic lung diseases. Disturbances of the intestinal microbiota in early life can increase the risk of developing asthma. The intestinal microbiota also protects against respiratory infections. Decreased intestinal microbiota will interfere with the immune response as the viral or bacterial infection progresses in the respiratory tract, as shown in Figure 4. Intestinal microbiota plays a role in the formation and response of antibodies. Decreased intestinal microbiota due to antibiotic therapy can increase the number of bacteria in the blood and increase mortality.[1,3,4]

The concept of the gut-lung axis is a bidirectional interaction, a circle that can be stimulated from two sides.[1,10,17] The epithelial surfaces of the gastrointestinal tract and respiratory tract are exposed to various kinds of microbes. Ingested microbes can enter the gastrointestinal tract and then, through aspiration, can

enter the respiratory tract.[2,5,9] The intestinal and lung mucosa work as defenses against microbial penetration. Colonization between normal microbes and pathogenic microbes will stimulate an inflammatory response.[5] The transmission of commensal bacteria in the intestine, such as SFB, *Bifidobacterium*, and members of the genus *Bacteroides* also induces the formation of antimicrobial peptides, immunoglobulin A, and inflammatory cytokines.[5–7,15,16]

The lung microbiota is vital in the maturation and homeostasis of lung immunity. Colonization of the respiratory tract provides an important signal for local immune cell maturation. Pre-clinical studies have demonstrated a causal relationship between microbial colonization in the airways and regulation and maturation of immunity in the airways.[7]

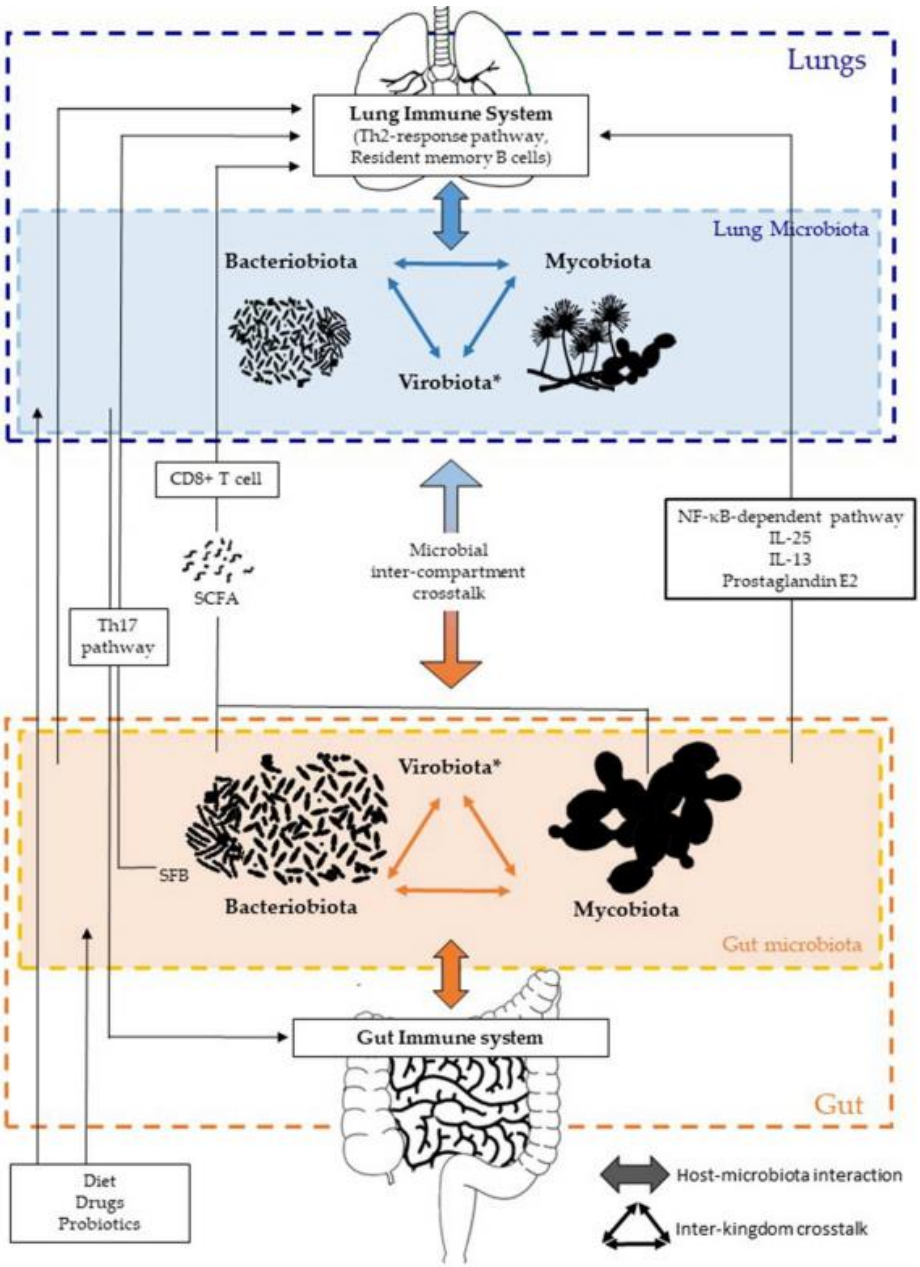


Figure 5. Inter-kingdom and inter-compartment in gut-lung axis[7]

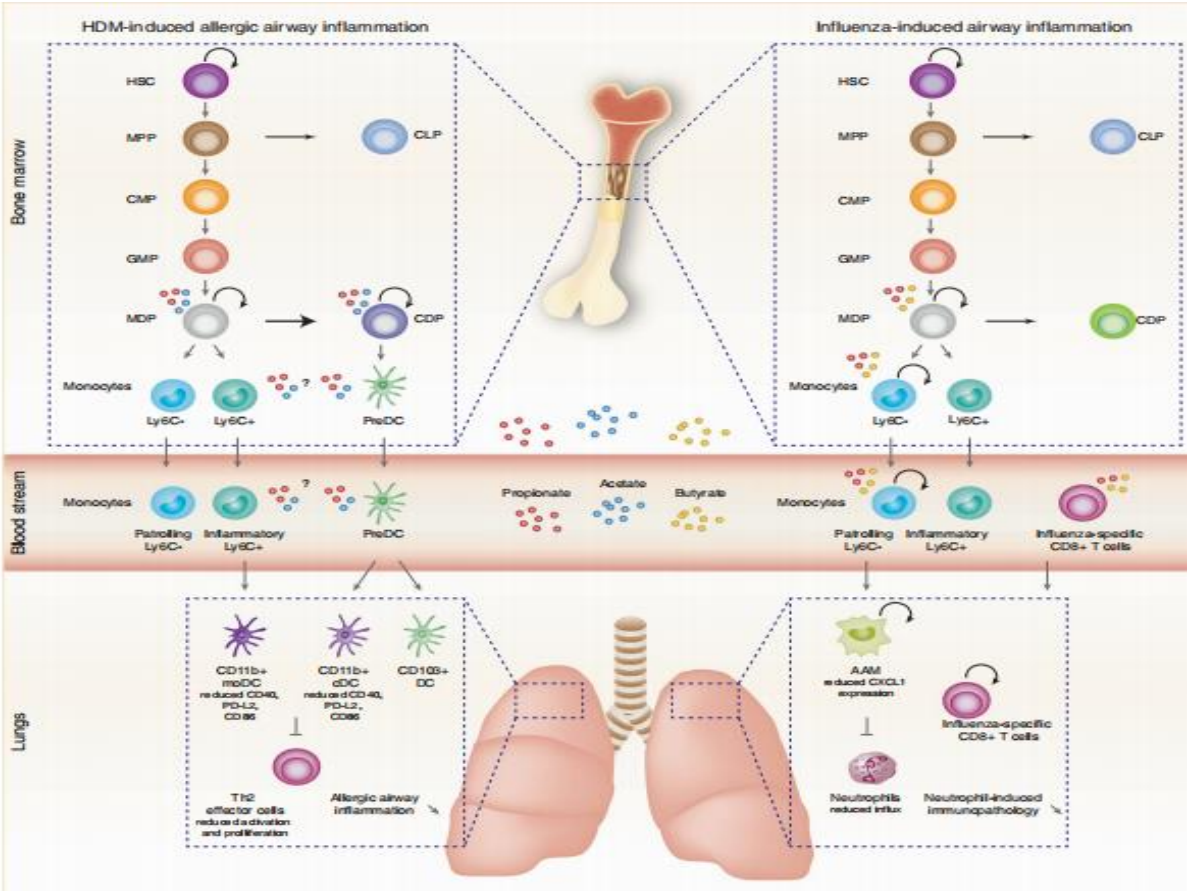


Figure 6. The effect of short chain fatty acid in bone marrow[2]

Figure 5 shows the relationship between components of the gut-lung axis system. Microbes interact with each organ via direct or indirect mechanisms. Intestinal microbes affect the immune system in the gut and lungs through local interactions or long-term interactions involving CD8+ T cells, Th17, IL-25, IL-13, prostaglandin E2, and NF-kB-dependent pathways. Lung microbiotas influence mucosal immunity and contribute to immune tolerance through neutrophil uptake, pro-inflammatory cytokines production mediated by receptor 2 (TLR2), and release of antimicrobial peptides such as Th17-stimulated β-defensin 2.[7]

Microbiota also produces metabolites. Fiber fermentation by gut microbiota produces short-chain fatty acids, with the most common types being propionate, acetate, and butyrate. These fatty acid products spread from the intestines to the bloodstream and can reach the bone marrow to stimulate the process of hematopoiesis. In the bone marrow, hematopoietic stem cells (HSCs) can differentiate into multipotent progenitors (MPPs), as shown in Figure 6. Furthermore, MPPs will differentiate into common lymphoid precursors (CLP), common myeloid precursors (CMP), granulocyte and macrophage precursors (GMP) and monocyte and DC progenitor (MDP).[2]

The MDP precursors will differentiate into monocytes such as Ly6C+, Ly6C-, and common dendritic cell precursor (CDP). When inflammation occurs, Ly6C+ cells will turn into CD11b high monocyte-derived

DCs (CD11b+ moDC), while CDP becomes pre-classical dendritic cells (pre-DC). Pre-DC cells will migrate from the bone marrow to the lungs and undergo maturation to become CD11b+ cDC. These maturation cells have a high phagocytic function but are less activated due to decreased expression of CD40, PD-L2, and CD 86. Thus, the ability of these lung DC to induce Th2 function and proliferation is decreased.[2]

Intestinal microbial diversity in early life may reduce inflammation in the airways mediated by the Th1 or Th2 balance. Another study used stool samples from pediatric patients diagnosed with asthma and healthy children as controls. In the asthma group, increased levels of inflammatory factors including CRP, TNF-α, IL-6, and decreased numbers of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* bacteria were discovered. These bacteria can suppress inflammation by increasing IL-10 and decreasing IL-12. This indicates that increased levels of inflammatory factors are associated with dysbiosis in the gut and increase the risk of asthma.[3,11]

Microbiota in the gut and lungs are important in fighting bacterial pneumonia. Lung microbiota plays a role in protecting tissues against infection by *Streptococcus pneumoniae* and *Klebsiella pneumoniae* by forming granulocyte-macrophage colony-stimulating factor (GM-CSF), which IL-17 stimulates. The gut microbiota also plays a role when a bacterial infection occurs in the lungs. Studies in mice have shown increased morbidity and mortality during acute lung infection by *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, or *Pseudomonas aeruginosa*. The use of broad-spectrum antibiotic therapy can disrupt the gut microbiota in mice and result in poorer outcomes.[2,6]

In COVID-19, gastrointestinal and respiratory tract disorders often coexist. Researchers then analyzed the gut microbiota of COVID-19 patients. The results found that in COVID-19 patients, the number of *Bifidobacterium*, *Lactobacillus*, and *Eubacterium* decreased. At the same time, pathogenic bacteria such as *Corynebacterium* (*Actinobacteria*) and *Ruthenibacterium* (*Firmicutes*) increased significantly. As the patient gets older, the diversity of the gut and lung microbiota decreases. Gut microbiota is impaired due to decreased function in elderly patients. These change in composition causes an imbalance in the microbiota and makes the immune system to weakened.[4,9]

The immune response induced by a viral infection in COVID-19 alters the gut microbiota leading to dysbiosis and increased intestinal permeability. This leads to secondary infections such as bacterial pneumonia. Under these conditions, increased intestinal permeability allows bacterial antigens and toxins to be translocated through the systemic circulation. This leads to sepsis and respiratory failure syndrome, due to dysfunction of the respiratory tract barrier. Another study by Vincent JL stated that endotoxin in patients with severe COVID-19 would increase. Gram-negative bacteria produce the toxin in the intestines.[18]

PROBIOTICS AND DIET ON THE GUT-LUNG AXIS

The gut microbiota can be affected by diet and lifestyle. Compared to an agrarian diet that consumes a diet low in fat and high in vegetables, a Caucasian diet high in fat and sugar content shows a significant decrease in *Bacteroidetes*. Children from Africa with a diet high in protein and fiber had higher levels of *Actinobacteria* and *Bacteroidetes*. Children from Western Europe with a high-fat and low-fiber diet showed higher levels of *Firmicutes* and *Proteobacteria*. SCFA content was four times higher in African populations with high concentrations of bacteria such as *Prevotella*, *Butyrivibrio*, and *Xylanibacter* to ferment polysaccharides from dietary fiber. The increase in SCFA causes a decrease in pH in the intestines, thereby reducing the number of pathogenic bacteria such as *Escherichia coli* and *Enterobacteriaceae*.[19]

Many studies have been conducted to evaluate the function of probiotics in the immune system. Research in mice indicates that T_{reg} cells that reduce allergic responses can be induced by administering probiotic bacteria such as *Lactobacillus rhamnosus*, *Bifidobacterium lactis*, and *Bifidobacterium breve*. The administration of *Lactobacillus casei shirota* or *Lactobacillus rhamnosus* in cystic fibrosis patients showed a decrease in symptoms of exacerbations. Probiotics also improve inflammatory conditions in Irritable Bowel Disease (IBD) patients by regulating innate immunity through TLR. Probiotics increase the defense function in the intestine by producing bactericidal substances that will fight pathogenic bacteria.[1,19]

CONCLUSION

Microbiota plays a role in the formation and maturation of the immune system. In contrast, the immune system shapes the composition and function of the microbiota that influence the inflammatory response in the body. The gut-lung axis is the interaction between the gut and the lungs. Changes in the composition of the gut microbiota not only cause abnormalities in the intestine but also affect other organs such as the lungs and cause diseases in the respiratory tract. Through these interactions, an approach through the gut microbiota could be useful in the management of pulmonary diseases.

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