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Review article

People are an organic unity: Gut-lung axis and pneumonia

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A B S T R A C T

People are an organic unity. Every organ of our body doesn't exist alone. They are a part of our body and have important connections with other tissues or organs. The gut-lung axis is a typical example. Here, we reviewed the current research progress of the gut-lung axis. The main cross-talk between the intestine and lungs was sorted out, i.e. the specific interaction content contained in the gut-lung axis. We determine a relatively clear concept for the gut-lung axis, that is, the gut-lung axis is a cross-talk that the gut and lungs interact with each other through microorganisms and the immune system to achieve bidirectional regulation. The gut and lungs communicate with each other mainly through the immune system and symbiotic microbes, and these two pathways influence each other. The portal vein system and mesenteric lymphatics are the primary communication channels between the intestine and lungs. We also summarized the effects of pneumonia, including Coronavirus disease 2019 (COVID-19) and Community-Acquired Pneumonia (CAP), on intestinal microbes and immune function through the gut-lung axis, and discussed the mechanism of this effect. Finally, we explored the value of intestinal microbes and the gut-lung axis in the treatment of pneumonia through the effect of intestinal microbes on pneumonia.

1. Introduction

the gut-lung axis is a cross-talk that the gut and lungs interact with each other through microorganisms and the body's immunological function to achieve bidirectional regulation. The gut-lung axis was first proposed in 1991 by Pugin et al. [1]. Except for typical respiratory symptoms, digestive system symptoms are also prevalent in patients with Coronavirus disease 2019 (COVID-19). with the COVID-19 global outbreak, the gut-lung axis turned into a hot topic. That the function of the gut-lung axis was widely recognized provides convincing proof for the body's overall concept.

The gut-lung axis literally consists of four main parts: Lung disease causes changes in gut flora; Lung disease can be influenced by the regulation of intestinal flora; Intestinal diseases can cause changes in lung flora; regulating the lung flora can have an effect on diseases of the intestinal tract. Before the application of bronchoscopy, it was widely believed that the lungs were sterile [2]. It wasn't until the first report that the airway bacterial density resembled that in the small bowel that widespread attention began to be paid to the lung microbiome [3]. Therefore, the current research status of the gut-lung axis mainly focuses on the interplay among intestinal microbes and pulmonary diseases. Observational studies mainly explore changes in gut microbiota following respiratory disease or lung injury [4–6]. Experimental study focuses on the therapeutic effect of intestinal intervention on lung disease [7–9].

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Gut-lung axis is an abstract pathway connecting the intestine and lungs with the portal vein system and mesenteric lymphatic vessels [10–12] as specific channels, realizing the communication between immune function and symbiotic microorganisms, and widely participating in a variety of lung diseases. Especially during the COVID-19 pandemic, there was a substantial increase in the number of studies on the gut-lung axis. Although the epidemic has now subsided, various types of pneumonia, especially Community-Acquired Pneumonia (CAP), remain a critical clinical community fitness issue. numerous people infected with CAP annually, with a wide range of impacts. Research has shown that 1 to 25 people suffer from CAP every 1000 residents each year [13]. Antibiotics are its main therapeutic agents, but the rate of drug resistance is rising every year. At the same time, due to the important role of immune communication in the gut-lung axis, the inflamed reaction in the lungs is inevitably linked to this. Because of the limited space of this article, we focus on the most representative COVID-19 and CAP in pneumonia to specifically describe the functions played by the gut-lung axis. The key points of communication in the intestinal tract and airways on the strength of the gut-lung axis as the hub are discussed from two directions respectively: from the lung to the gut and from the gut to the lung. It is expected to offer fresh insights and methods for the therapy of lung-related diseases.

2. Immune crosstalk in the gut-lung axis

Both the intestine and lungs contain a mucous membrane made up of epithelium and lamina propria. The respiratory tract and intestinal immune response all belong to the domain of mucosal immunity. The mucosal immunity of all parts of the body is closely related and is called the common mucosal immunological system (CMIS) [14]. The mucous membrane has secretory immunoglobulin A (SIgA) secreted by the plasma cells transformed from B cells. Antigen-specific T and B cells are produced in the local mucosa after being stimulated by antigen. They migrate out of the initial site of local immune response and eventually home to different mucosal

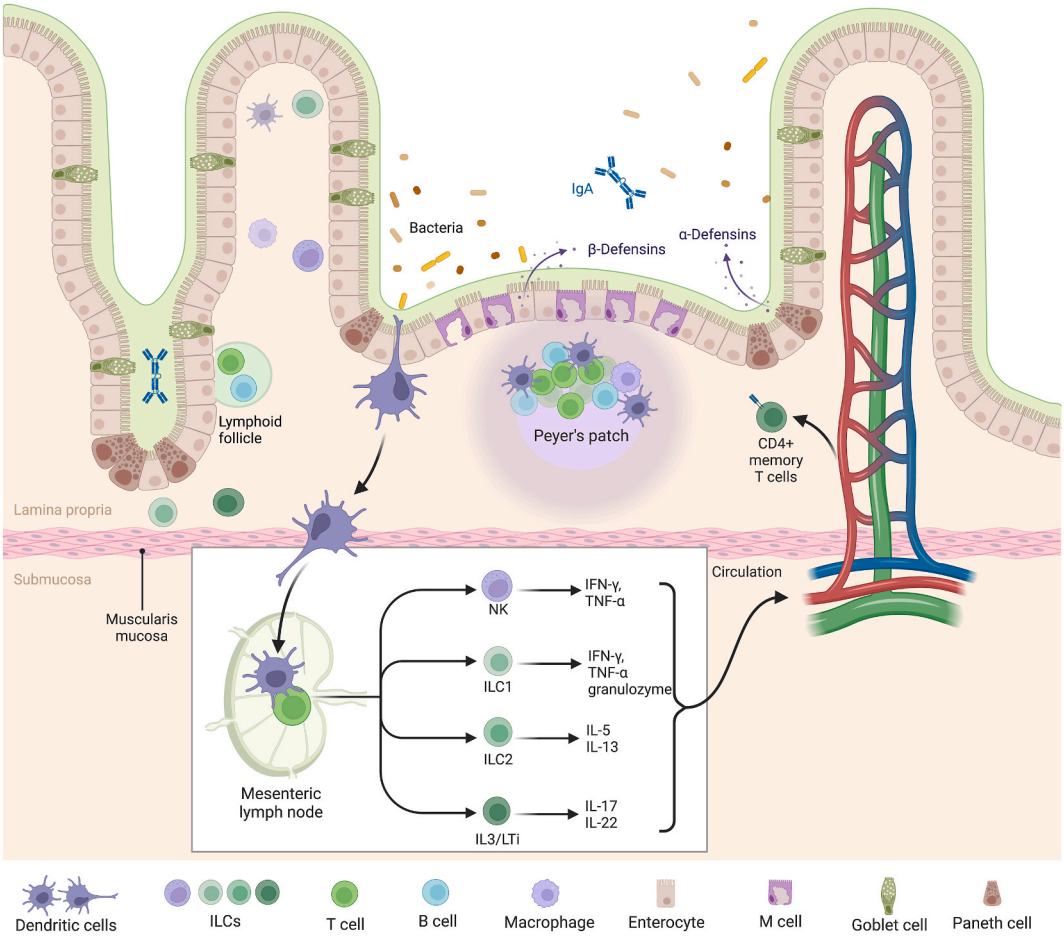

Fig. 1. Immune crosstalk of gut-lung axis. Immune cells such as DCs and lymphocytes are activated by intestinal microbes and enter lymphatic and blood circulation through mesenteric lymphatics and portal vein system, and finally enter the lung to play an immunomodulatory role. The CMIS of the intestine contains SIgA secreted from plasma cells. Antigen-specific T and B cells are produced after the local mucosa is stimulated by antigen, which jointly induces the mucosal immune response. GALT includes lymphocytes between intestinal epithelial cells and lamina propria, Peyer's node, independent lymphatic follicles in the gut, mesenteric lymph nodes, SIgA, α- Defensins and β- Defensins. Together, they play an immunomodulatory role.

effector sites in the body, play an immune response against the same antigen, and guide a mucosal immunity reaction. Part of the proplasmacyte generated in the intestinal mucosal lymphoid tissue accesses the respiratory mucosa through the blood circulation and produces SIgA, which plays an immune role similar to that of the intestinal lymphoid tissue, constituting a component of immunity communications of the gut-lung axis and making intestinal immunity a part of the systemic immunity. In addition, the recycling of mucosal lymphocytes, the migration and homing of immunocytes for example innate lymphoid cells (ILCs), T helper (Th) 17 cells, and dendritic cells (DCs) are also the main means of communication between the intestine and the lung in the CMIS (Fig. 1).

ILCs are a kind of leukomonocyte without expressing antigen receptors and are located on mucosal surfaces, most of which are tissue-resident cells [15]. It is crucial to tissue homeostasis and the starting of an immune reaction [16] and is the primary barrier for mucosal defense against infection. ratified by the International Union of Immunological Societies (IUIS), ILCs were composed of five subgroups according to their growth and feature: Natural killer (NK) cells, ILC1, ILC2, ILC3, and lymphoid tissue-inducer (LTi) cells [17]. NK cells mainly exist in secondary lymphatic tissue, circulation, and some peripheral organs, while ILC1 is mainly distributed in the liver, salivary glands, small intestinal epithelial and lamina propria, uterus, and adipose tissue of the internal organs [18]. NK cells and ILC1 mainly produce interferon γ (IFN-γ), tumor necrosis factor α (TNF-α), and mediators of cytotoxicity, e.g., granzymes. ILC2 is widely distributed in barrier tissues [19], including blood, lymphatic tissue (for example the spleen, bone marrow, and mesenteric lymph nodes), non-lymphoid tissue (liver, kidney, visceral adipose tissue, etc.), and mucosal tissue (such as lung, intestinal mucosa, etc.). ILC2 produces type 2 cytokines such as interleukin-5 (IL-5) and IL-13. ILC3 and LTi mainly exist in the lamina propria of the small intestine and generate IL-17 and/or IL-22. The functions of ILC1, ILC2, and ILC3 are similar to those of $CD4^+$ Th1, Th2, and Th17, respectively. ILC1 can resist pathogens in cells, i.e., viruses and tumors. ILC2 reacts to parasites out of cells and allergens. ILC3 can target extracellular microorganisms, i.e., bacteria and fungi. NK cells reflect the function of $CD8^+$ cytotoxic T cells. LTi cells are essential in the generation of the peripheral lymphatic organization and organs [17] (Fig. 2).

Although ILCs are tissue-resident cells, they can migrate through lymphatic homing and form a part of the main communications in the gut-lung axis. ILC3 can translocate to mesenteric lymph nodes (MLN) from the lamina propria of the small intestine. Inflammatory ILC2 and NK cells can enter the blood circulation. ILCs preferentially homing to mucosal tissues, and ILC2s, ILC3s, and Th17 achieve the migration of intestinal and pulmonary immune cells through lymphocyte homing [20,21]. The study showed that IL-25 activated the IL-17RB (IL-25 receptor) expressed by intestinal ILC2 in mice after being infected with *Nippostrongylus brasiliensis.* Activated intestinal ILC2 (also known as "inflammatory" ILC2) then left the intestine in a manner dependent on Sphingosine 1 phosphate ester receptor 1 (S1PR1) and migrated to the respiratory tract to enhance type 2 immunity in the lungs [22]. A part of intestinal ILC2 entering the lung up-regulated the ST2's expression, ST2 was the receptor of IL-33 and also called IL-1RL1, thus exhibiting a lung-resident ILC2 phenotype [23]. Similarly, under the stimulation of IL-25 or worms, ILC2 located in the lamina propria of the intestine can also transfer to the pulmonary tissue through mesenteric lymphatics, and support pulmonary anti-worm and tissue repair [20]. In lung infection mediated by *Klebsiella pneumoniae*, CC chemokine receptor 2(CCR2) -positive inflammatory monocytes recruited to the pulmonary tissue secreted TNF-α, TNF-α promoted the gathering of intestinal ILC3 to the lung infection site and the secretion of IL-17A by up-regulating the expression of chemotactic gene ligand 20 (CCL20) in pulmonary epithelial cells, Thus, the uptake and killing of bacteria mediated by monocytes were enhanced [24]. At the same time, ILCs subgroups also exhibited some plasticity, that is, mature ILCs can be transformed into other ILCs lineages to deal with local immune reactions. It is proven that ILC2, ILC3, and NK cells can transform into functional ILC1 or ILC1-like cells [17,25–30]. This provides more possibilities for the communication of ILCs between the gut-lung axis.

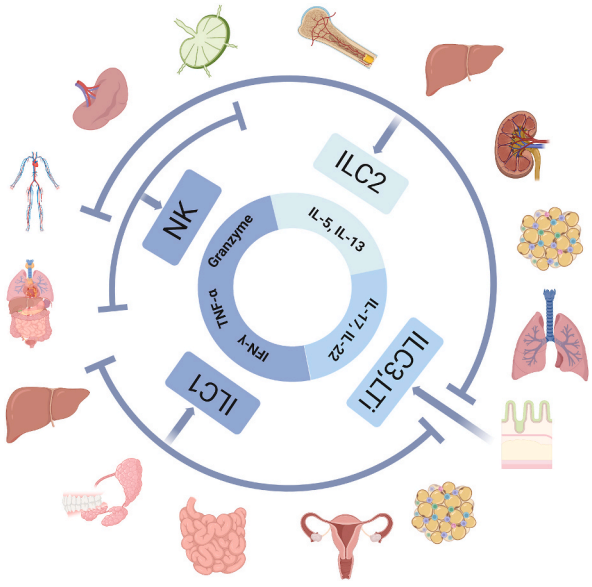

Fig. 2. Innate lymphoid cells tissue or organ distribution and their products.

In addition to ILCs, Th17 cells, which are functionally similar to ILC3, are also important components of CMIS. The intestinal lamina propria is the main residence of Th17 cells. Th17 cells are produced in response to the microbiota [31], and the gut flora can regulate its structure and function [32]. Current studies showed that segmented filamentous bacteria (SFB) were the main bacterial inducers. Th17 cells are also present in the intrapulmonary mucosa, as well as SFB-induced intestinal Th17 cells are preferentially recruited to the lungs due to the strong expression of the Th17 chemoattractant CCL20 in the lungs, thus causing distal lung lesions [21]. So Th17 cells constitute an essential part of the immune communication of the gut-lung axis. Under current studies, Th17 cells can exhibit both beneficial and pathogenic effects, depending on the specific biological circumstances. On the one hand, polarized Th17 cells have effects on anti-infection and maintenance of intestinal epithelial integrity to preserve intestinal homeostasis. Th17 cytokines IL-17A, IL-17F, and IL-22 stimulate the production of mucins and antimicrobial peptides, increase intestinal epithelial tight junctions, and up-regulate polymeric immunoglobulin receptor (pIgR) expression to increase the transport of IgA into the lumen, thereby enhancing anti-microbial defenses and enhancing barrier function [33–35]. Meanwhile, direct or indirect effects of IL-17 significantly stimulate neutrophil maturation, migration, and function in lung tissue and airways. IL-17-induced neutrophil activation and migration are critical for defense against various pathogenic organisms that infect the lungs [36,37]. On the other hand, when exposed to IL-23, Th17 turns into pro-inflammatory cells [38]. Increased neutrophil aggregation is also a double-edged sword, and studies have shown that smoking-induced local pulmonary Th17 responses lead to increased systemic susceptibility to inflammatory injury by enhancing circulating neutrophils [39]. IL-17A exacerbates asthma-induced intestinal immune damage by promoting neutrophil transport [40]. In addition, Th17 cells are also involved in various autoimmune diseases, and their pathogenic role in inflammatory bowel disease has been well established [41]. Th17 has also been reported to be a key participant in psoriasis, Rheumatoid arthritis, Crohn's disease, Ulcerative colitis, multiple sclerosis, and Ankylosing spondylitis [33,42,43].

The role of commensal microorganisms in regulating the balance of pro-inflammatory and anti-inflammatory cells is also an important topic. The "gut-lung axis" theory demonstrated that pneumonia could lead to intestinal bacterial dysbiosis and Th17/Regulatory T cells (Treg) cells immune imbalance [44]. Both Th17 and Treg are differentiated from the naïve CD4 T cell [45], and are most abundant on the mucosal surface, especially in the intestinal lamina propria. Th17 cells induce autoimmunity and inflammation, whereas Treg cells suppress these processes and maintain immune homeostasis. Thus, they play opposite roles in inflammation and immune responses [46]. It was demonstrated that disrupting the balance of Th17/Treg cells could exacerbate LPS-induced inflammatory lung injury [47]. Commensal microorganisms can regulate the Th17/Treg balance, which modulates the local inflammatory response. Research by Wu, Y. et al. indicated that probiotics could promote the balance of Th17 and Treg cells in PM2.5-induced lung injury, inhibit the expression of pro-inflammatory cytokines TNF-α, IL-6, IL-1β, and IL-17A, and increase the concentration of anti-inflammatory factors such as IL-10 and transforming growth factor beta (TGF-beta) [48]. Consistently. fecal microbiota transplantation (FMT) restored the balance of Th17/Treg cells in *Pseudomonas aeruginosa* pneumonitis mice and ameliorated inflammation and lung injury by modulating intestinal flora and metabolic disturbances [44]. Latest studies have shown that the gut microbial tryptophan metabolite indole-3-acetic acid (IAA) has an important role in regulating Th17/Treg balance, which has been proven in both arthritis and ankylosing spondylitis treatment [49,50]. Treg, similar to Th17 cells, has both beneficial and pathogenic roles, depending on the specific biological setting. The complex interactions of microorganisms and their metabolites and the delicate balance of pro-inflammatory and anti-inflammatory cells in the immune system exemplify the sophisticated regulation of the human being as an organic unity and remain a great challenge for future research.

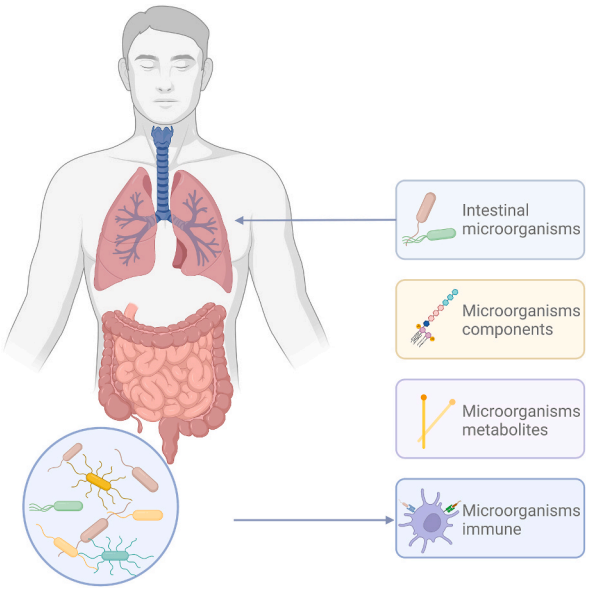

Fig. 3. Gut microbes are involved in the crosstalk of the gut-lung axis in the following four ways: Direct migration of intestinal microorganisms, components from symbiotic microorganisms, metabolites of microorganisms, and Immune regulation involving microorganisms.

3. Microbial crosstalk of the gut-lung axis

The intestinal symbiotic microbiota, known as "forgotten organs", has about 1014 kinds of bacteria, consisting of about 40 trillion bacteria, and is the largest microbial community in our body [51,52]. These microorganisms have co-evolved with our bodies and formed a symbiotic relationship. Intestinal symbiotic microbes influence the immunity reaction of the lungs, and microbes' imbalance affects the progress and recovery of human diseases. With the progress of research, the presence of the gut-lung axis was proved in both mice and humans, and many lung diseases are affected by changes in intestinal microbiota [53–56]. In 2005, Eckburg et al. found that intestinal microbiota mainly included six phyla of *Firmicutes, Bacteroides, Proteobacteria*, *Actinobacteria, Verrucomicrobia,* and *Fusobacteria*, in which *Bacteroides* and *Firmicutes* were the main dominant bacteria groups [57,58]. Intestinal microorganisms are significant in human health, especially in the immune system development and maintaining [59]. Symbiotic microbes and their metabolites can enhance immune function and promote anti-inflammatory reactions to establish an efficient and balanced immune system. The effective activation of innate immune response and adaptive immune response depends on the intact intestinal microbiota [60,61]. Intestinal pathogenic microbes encounter symbiotic microbes when attacking the host, which may affect their infection of the host. For example, the unique SFB can resist rotavirus infection of the intestinal epithelium [62,63]. Host-microbial interactions not only have local effects but also influence distal organs and tissues, for example, the lungs. Gut microbes are involved in gut-lung axis communication in the following four ways (Fig. 3).

3.1. Direct migration of intestinal microorganisms in the intestine and lungs

The mesenteric lymphatic system is an important channel for the gut-lung axis. Complete bacteria, bacterial fragments, and products of their metabolism (for example Short-Chain Fatty Acids, SCFAs) can migrate across the gut via the mesenteric lymphatic system and enter the circulatory system, thus regulating the immunological reactions of the lungs. In sepsis mouse models and people with acute respiratory distress syndrome (ARDS), lung microorganisms are rich in intestinal germs. Ecologic profiling showed that the inferior digestive tract instead of the upper airways was the main possible origin of pulmonary bacteria after septicemia [64].

3.2. Components from symbiotic microorganisms

The components from symbiotic microorganisms are the microbe-associated molecular pattern (MAMP). It includes bacterial polysaccharide (PSA), peptidoglycan, flagellin, lipopolysaccharide (LPS), and nucleic acid structure of microorganisms. PSA guides cellular and physical maturation during the development of the immune system [65,66]. LPS is the essential ingredient of the gram-negative bacterial cell wall, which stimulates the Toll-like receptor 4 (TLR4) on the epithelial cell membrane and activates the innate immune response of the body. rectal injection of LPS enhanced the protective effect of the immune system in mice treated with an antibiotic (without intestinal microbiota) infected with the influenza virus [67]. In conclusion, the components derived from symbiotic microorganisms participate in and maintain the host mucosal innate immune response as MAMP [68].

3.3. Metabolites of microorganisms

The metabolites of microorganisms mainly include SCFAs, desaminotyrosine (DAT), Indole derivatives (aryl hydrocarbon receptor ligand-indole-3-aldehyde), niacin, Urolitin A, lactic acid and pyruvic acid. Intestinal microbial imbalance can cause changes in circulating microbial metabolites, resulting in immune disorders and systemic inflammation. Long-term reduction of microbial metabolites may lead to persistent symptoms. DAT can protect the host from virus infection by promoting the effect of IFN-1 and reducing the lung immunopathology to protect the host against influenza [69]. Indole derivatives can enhance mucosal immunity [70]. Niacin is also produced by intestinal microbes and inhibits intestinal inflammation [71]. Uridine A protects intestinal epithelium from colon diseases by strengthening the barrier function and reducing inflammatory response [72]. Lactic acid and pyruvate enhance the immune response and improve resistance to *Salmonella enterica* [73].

SCFAs are the most important metabolites of symbiotic microorganisms. SCFAs mainly come from the metabolism of dietary fiber by cecum and colon microbes, including acetate, propionate, and butyrate. SCFA can be brought into circulation by passively diffusing and active transport. the active transport is mainly mediated by transport proteins, i.e., monocarboxylate transporter 1 and 4 (MCT1, MCT4) and sodium-coupled monocarboxylate transporter 1 and 2 (SMCT1, SCMT2) [74]. There is definite evidence that SCFA affects the hematopoietic function of bone marrow and accelerates the macrophages and DC precursors to generate [75]. The basic function of SCFA is to reduce the pH value of the intestine and promote the synthesis of mucin, thus preventing the pathogenic bacteria to grow and adhere, enhancing epithelial integrity, and the immunity of the host system [76,77]. SCFAs work mainly in two ways. First, SCFAs bind to G protein-coupled receptor (GPR), including GPR43 (also called free fatty acid receptor 2, FFAR2), GPR41 (FFAR3), and GPR109A (NIACR1). SCFAs are agonists of FFAR2, FFAR3, and GPR109A. FFAR2, FFAR3, and GPR109A are major expressed in immune cells, the pancreas, the spleen, and adipose tissue. FFAR2 may be the main receptor of SCFA's influence on inflammation and immune diseases. FFA2 receptor activation is associated with Gαi and Gαq, reduced cAMP levels, and increased cytoplasmic calcium concentrations, and is related to the prevention of acute and chronic respiratory diseases [78]. The FFA2 receptor is also involved in the regulation of β- Inhibin-2 mediates another signal routing by inhibiting NF-κB producing anti-inflammatory action [79]. For instance, butyric acid and propionic acid can inhibit monocytes induced by LPS to express TNF-α and nitric oxide synthase (NOS) [80]. During airway inflammation, SCFA reduces the production of IL-8 by neutrophils and macrophages through the activation of FFA2 and FFA3 [81]. Butyrate reduced the production of inducible NOS (iNOS), TNF-α, monocyte chemoattractant protein 1 (MCP-1), and IL-6

by activating FFA3 on macrophages [82]. The administration of propionic acid esters in allergic mice can reduce inflammatory mediators in the lungs, i.e., IL-4, IL-5, and IL-17A, by the FFA3 receptor dependent approach [83]. Second, SCFAs are also an inhibitor of histone deacetylase (HDAC). HDACs and histone acetyltransferases (HAT) regulate the acetylation of histones, and butyrate is the most effective HDAC inhibitor, which is implicated in the expression of inflammatory genes, regulation of vascular integrity, and progression of cardiovascular illnesses [80]. Butyrate, as well as propionate, inhibit inflammation by inhibiting the generation of HDACs by macrophages and DCs. For example, butyric acid and propionic acid inhibited TNF-α production and NF-κB function by inhibiting HDACs and stimulated the generation of the anti-inflammatory mediator IL-10 in lipopolysaccharide-activated monocytes and neutrophils [79] (Fig. 4).

3.4. Immune regulation involving microorganisms

The two pathways that make up the gut-lung axis, the symbiotic microorganisms and immune responses in the intestine often interact with each other. Research has revealed that mice treated with antibiotics cause an increase in ILC2 by depleting the symbiotic microbes in the gut [84]. Therefore, it is suggested that intestinal microbiota may inhibit the amount of ILC2 in the human gut. Intestinal microbial disturbance can lead to the stimulation of mucosal innate immune cells, composed of ILC2s, ILC3s, and Th17, through the interaction with DCs [32,85]. The exposure of intestinal symbiotic bacteria during the specific growth window of the neonatal period is necessary for the strong body's defensive capability to the resistance of bacterial pneumonia (the main reason for infant death) and is important for lung mucosal immune development in mice. Neonatal mouse intestinal CD103 + CD11b + DCs capture antigens from the symbiotic bacterium, and lung homing signal CCR4 on IL-22 + ILC3 is induced to express. This promotes the transport and accumulation of IL-22 + ILC3 to the lung and promotes lung IL-22-dependent mucosal defense. Increased resistance of newborn mice to pneumonia. The destruction of symbiotic microorganisms can cause lasting changes in the function of pulmonary immunocyte-producing IL-22 in neonatal mice, thus enhancing vulnerability to pneumonia [86]. Effective Nod-like receptor-activated bacteria (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and microorganisms in the gut (*Lactobacillus reuteri, Enterococcus faecalis, Lactobacillus crispatus, and Clostridium orbiscindens*) in the upper airway enhance the lung's resistance to infection through Nod2 and granulocyte-macrophage colony stimulating factor (GM-CSF). The microbiota increases the levels of GM-CSF in the lung through IL-17A. The GM-CSF signal stimulates alveolar macrophages to kill and remove pathogens through extracellular signal-regulated kinase signal, thus enhancing the immunity function of the airways and protecting the host to resist infection in the lungs caused by the *Streptococcus pneumoniae* and *Klebsiella pneumoniae* [87]. *Helicobacter pylori* extract can improve the symptoms of allergic asthma by inducing Batf3-dependent intestinal $CD103^{+}CD11b$ DCs to accumulate and secrete IL-10 in the lungs [88]. Expression of transcription factor ZBTB46 in $CCR6^{+}$ ILC3 is influenced by the gut microbiota and inflammatory response. ZBTB46 can inhibit the intestinal inflammation of rodents infected with *Citrobacter* and protect and enhance intestinal tolerance [89,90]. Non-infectious *Salmonella* in the intestine can restrict the function of the NF-κB pathway by reducing the ubiquitination of IκBα in epithelial cells, thereby reducing the immune inflammation [91].

4. Gut-lung axis and intestinal mucosal barrier

The mucosal barrier in the gut is also essential for communication between the gut-lung axis. Ischemia, hypoxia, and immune regulation induced by lung diseases can damage the intestinal mucosal barrier. The intestinal mucosal barrier must remain intact because it is a crucial prerequisite for the body to resist the transfer of bacteria, toxins, and other hazardous materials in the intestine. Intestinal symbiotic microbiota, a participant of the gut-lung axis, is also important for the construction and sustaining of the intestinal barrier. The intestinal barrier includes intestinal symbiotic microorganisms (biological barrier), mucus layer containing various host defense molecules (chemical barrier), columnar intestinal epithelial cell layer and its tight connection (mechanical barrier), and intestinal-associated lymphoid tissue (GALT) (immune barrier) [66,92] (Fig. 1). The major role of the intestinal barrier is to prevent the migration of bacteria and harmful substances across the intestine. Intestinal beneficial bacteria can maintain and strengthen the barrier function of the intestine through various pathways [93]. Intestinal symbiotic microorganisms can occupy intestinal epithelial

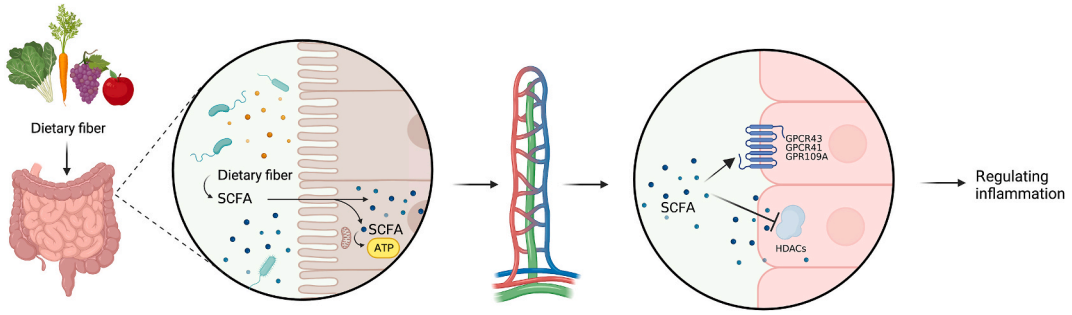

Fig. 4. Intestinal microorganisms produce SCFAs through the metabolism of dietary fiber. After SCFA enters the blood circulation, on the one hand, it can activate G protein-coupled receptors (GPCR43, GPCR41, and GPR109A) on peripheral tissue cells, on the other hand, it can suppress the HDAC activation and finally serves to regulate inflammation.

by the adhesion of Phosphowallic acid, form a layer of biofilm barrier, and prevent the adherence and colonization of pathogenic microorganisms to the intestinal epithelial surface. The disturbance of gut microorganisms will directly damage the biofilm barrier function. The mucous layer is composed of mucin secreted by intestinal goblet cells and intestinal epithelial cells, which not only facilitates the growth of intestinal symbiotic microorganisms but also binds harmful bacteria and prevents them from adhering to the epithelium. Symbiotic microorganisms in the intestine, *Lactobacillus, and Bifidobacterium* can increase the mucin to be secreted. Columnar epithelial cells and the intercellular tight junctions in the gut can prevent the shift of intestinal bacteria and large molecules such as toxins. Intestinal epithelial cells can also act as phagocytic cells to engulf and kill bacteria. Intestinal beneficial bacteria can increase the quantity and diversity of epithelial cells in the gut and increase the tight junctions between intestinal epitheliums.

GALT includes lymphocytes between intestinal epithelial cells and lamina propria, Peyer patches (PP), independent lymphatic follicles in the gut, and MLN. In addition to the immune effects of related lymphocytes, SIgA secreted by plasma cells, alpha-defensin (HD-5, HD-6) secreted by Paneth cells of the small intestine, and beta-defensin (hBD-1,hBD-2) released by intestinal epithelial cells can be immersed into the mucous layer to exert antibacterial and antiviral effects (Fig. 1) [94]. Defensins can regulate the components of the microorganisms, and the imbalance of microorganisms will also affect the secretion of defensins, thus affecting how the local immunity works [95]. In summary, the equilibrium of the host intestinal commensal microbiota is important for the maintenance of a healthy intestinal barrier and optimal immune homeostasis. An imbalance of microorganisms can damage the barrier in the gut, cause migration of intestinal bacterium and endotoxins, lead to inflammation, metabolic disorders, and malnutrition, and result in infection of multiple organs, including the lungs.

5. Gut-lung axis and pneumonia

High proportions of patients with COVID and CAP presenting with intestinal symptoms have brought the gut-lung axis into increasing focus. A meta-analysis including 60 trials involving 4243 participants showed that 17.6% of patients with COVID-19 presented with intestinal conditions, and the detection of viral RNA in fecal samples was observed in 48.1% of patients [96]. In another meta-analysis involving 35 studies and including 6686 COVID-19 patients, the overall incidence of gastroenterological symptoms was 15% [97,98]. Similarly, in a study of 124 children with CAP, diarrhea symptoms were present in about 24% and vomiting in 7.3% of cases [99]. On the other hand, patients suffering from Inflammatory Bowel Disease (IBD) had an increased prevalence of severe COVID-19 and bacterial pneumonia [100,101], and their risk of complications is also significantly increased [101–103]. Meanwhile, pneumonia is also one of the most frequent reasons for hospitalization of patients with IBD [104], And the hospitalization rate of elderly patients with IBD complicated by pneumonia is higher [105].

5.1. Gut-lung axis and COVID-19

5.1.1. COVID-19 can cause intestinal changes

COVID-19 induced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) brought human life to a standstill. This natural selection has put human health to a major test. COVID-19 is similar to H7N9, with typical clinical manifestations of pneumonia and cytokine storms. Numerous clinical trials have confirmed that except for respiratory symptoms, many COVID-19 patients show digestive symptoms, for instance, diarrhea, vomiting, and nausea. A large amount of SARS-CoV-2 virus RNA is common in fecal specimens of people with COVID-19 [106]. Characteristic SARS-CoV-2 viral particles were discovered in the rectum tissue of COVID-19 patients under an electron microscope. In addition, without obvious mucosal damage, many SARS-CoV-2 positive lymphocytes and macrophages were also found in the lamina propria. data directly showed that SARS-CoV-2 was actively replicated in the rectum of patients within the time of incubation, and this explains the SARS-CoV-2 fecal-oral transmission [107]. After SARS-CoV-2 attacks the alimentary canal, it may alter the intestinal commensal microorganisms. Yeoh et al. conducted shotgun sequencing of the DNA obtained from feces in people with COVID-19. They found a substantial distinction in the intestinal microbes of patients in comparison to normal subjects and related to cytokine levels and markers of inflammation. Imbalances in the gut microbiota after recovering from the disease may cause persistent symptoms, and these differences in the microbiota remain significant for at least 30 days after virus clearance [6]. The effect of COVID-19 on intestinal commensal microorganisms was also reflected in another lasting 6 months prospective follow-up study of COVID-19 patients who underwent capsule endoscopy. COVID-19 patients had intestinal microbiota disorder and low intestinal fungal diversity, mainly Candida albicans. The bacterial diversity of severe patients is low, mostly shown as an uptick in *Enterococcus* and *Lactobacillus*, and a decline in *Faecalibacterium* and *Bacteroides*. There is a direct association between the level of *Candida* and *Enterococcus* in COVID-19 patients. Following the rehabilitation of critically ill patients, the diversity of bacteria still changed. However, the diversity of fungi returned, which was equivalent to heath people [108].

5.1.2. The mechanism of COVID-19 attacking the intestine

Exploration through relevant cellular and molecular experiments, the main cause of digestive system diseases coming from COVID-19 is that angiotensin-converting enzyme 2 (ACE2) receptors are the main targets of SARS-CoV-2 invasion. ACE2 receptor is mainly present in the respiratory tract, as well as highly expressed in the intestinal mucosa. ACE2 is a multi-dimensional transmembrane protein. SARS-CoV-2 mainly invades tissue cells through the interaction between the receptor binding domain of the viral spike glycoprotein and the ACE2 bounded with membrane, and then the complex of virus and ACE2 is internalized [109,110]. SARS-CoV-2 combines with cells in the gastrointestinal tract, such as epithelial cells of the intestinum tenue and intestinum crissum, through specific receptors such as ACE2 and transmembrane serine protease 2, resulting in the secret of cytokines and chemokines, and leading to acute intestinal inflammation symbolized by neutrophils, macrophages, and T-cell invasion. Effenberger, M. et al. demonstrated the

fact that SARS-CoV-2 infecting the host can cause intestinal inflammation, such as diarrhea, elevated Faecal calprotectin (mainly expressed by neutrophils), and systemic IL-6 response [111]. In addition, the infection of COVID-19 will cause the increase of 5-hydroxytryptamine (5-HT) secretion in the circulation. Enterochromaffin cells (ECs) in the gastrointestinal epithelium, account for about half of all enteroendocrine cells (EEs) cells and create nearly all the 5-HT in the human organism. EEs had the highest proportion of infections with SARS-CoV-2 in gastrointestinal epithelium cells 12 h after virus exposure. NRP1, ACE2, and TMPRSS2 are all SARS-CoV-2 receptors, among them, NRP1 is highly expressed in EEs. SARS-CoV-2 infection in cells expressing NRP1, ACE2, and TMPRSS2 increased more than three times. Only ECs can significantly express those three genes associated with SARS-CoV-2 in all kinds of intestinal cells. accordingly, EC-secreting 5-HT is highly infected by SARS-CoV-2 [112]. Intestine-derived 5-HT regulates intestinal peristalsis and intensifies inflammation by acting as chemokine of various immune cells and triggering cytokine release (Fig. 5).

5.1.3. *Influence of intestinal symbiotic microorganisms on COVID-19*

Numerous pieces of research indicated the component of gut flora in people with COVID-19 was changed [113–118]. In turn, these changes in the intestinal microorganisms were strongly correlated with the disease severity. The intestinal microorganisms participate in the occurrence of acute lung injury in COVID-19 in several ways, comprising the direct microbial transmission from the gut to the lungs and the immunological regulation of metabolites relevant to microbes. Chen, Y. et al. 's study also confirmed that intestinal disorders are also related to COVID-19 rehabilitation [54]. For example, *Bacteroides* is one of the main symbiotic microbial populations in human intestines. *Bacteroides* turn dietary glycans and polysaccharides into energy through a fermentation mechanism. The richness of *Bacteroides* in the host gut provides numerous benefits to the human body [119]. Increasing the *Bacteroides* species in patients with COVID-19 down-regulates the expression of ACE2, consequently decreasing SARS-CoV-2's capacity for replication in intestinal cells and ultimately contributing to viral clearance [120]. The severe pathological changes of COVID-19 are the result of virus infection, additionally an abnormal host immunoreaction, for example, the immune system's massive release of cytokines, leading to uncontrolled inflammation and failure of various organs. An intestinal biological imbalance will result in pro-inflammatory effects, and also reduce the anti-inflammatory mechanism. Animal experimentations indicated the imbalance of microbiota associated with COVID-19 is typical of the absence of commensalism bacterium with immune-modulating capabilities. Symbiotic microbiota maintains intestinal immunological homeostasis by keeping the equilibrium in inflammatory responses (such as TH17 T cells and Treg) [121]. besides, commensalism bacteria maintain the intestinal barrier through multiple mechanisms. Increased permeability of the intestine raises levels of LPS in the blood, which promotes inflammation and thrombosis, two hallmarks of severe COVID-19. Intestinal commensalism bacteria maintain the integrity of tight connections and promote mucus production and antimicrobial peptide secretion to avoid the LPS and bacterium relocation via the enteric cavity to the mucosa and into the bloodstream [122]. The metabolites of intestinal symbiotic microorganisms are also significant in the recovery of COVID-19. For example, clinical trials have also confirmed that butyrate and secondary bile acid can reduce the harmful effects of LPS in the serum of patients with COVID-19 [123]. In people suffering from severe COVID-19 pneumonia, SCFA, and L-isoleucine biosynthetic pathways are absent, and fecal butyrate levels are

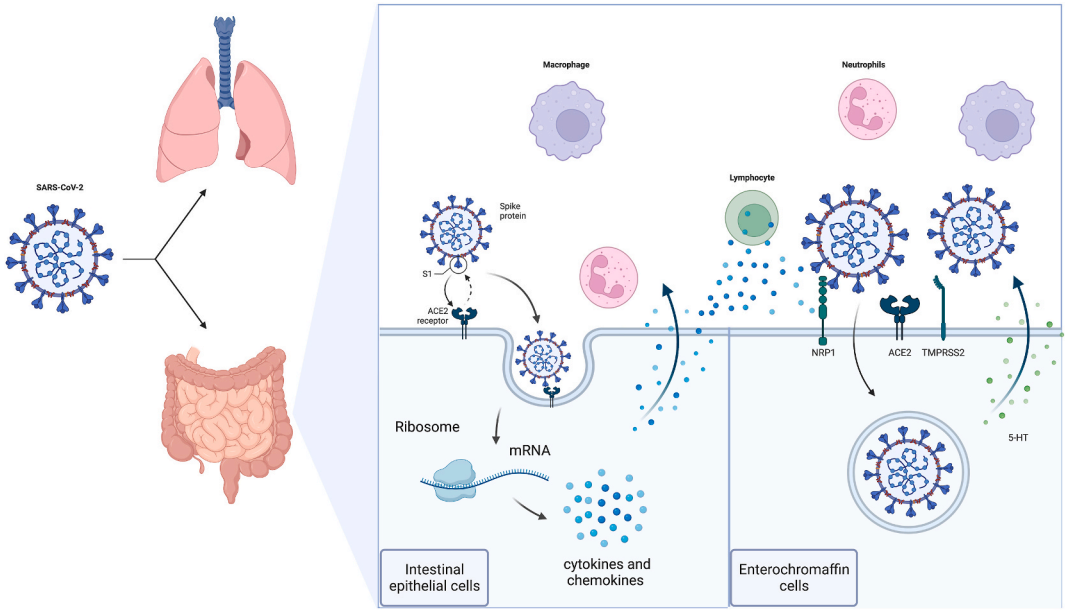

Fig. 5. ACE2 is a target of SARS-CoV-2 to attack the body, which is present not only in the lungs but also in the intestine. SARS-CoV-2 attacked intestinal epithelial cells through ACE 2, causing increased secretion of chemokines and cytokines, and eventually causing intestinal inflammation characterized by the accumulation of immune cells; ECs had NRP1, ACE2, and TMPRSS2, so their chance of infection by SARS-CoV-2 increased more than 3-fold, resulting in massive SARS-CoV-2 infection of the intestine.

reduced, resulting in increased plasma levels of the cytokine IL-10, C-X-C motif chemokine ligand 10 (CXCL10), and the acute phase reactant C-reactive protein (CRP). It finally causes the aggravation of COVID-19 [124]. Butyrate inhibits viral infection by decreasing the transcription of membrane ACE2 and increasing its shedding, as well as reducing the activation of viral spike proteins. The high-mobility group box 1 (HMGB1), which is necessary for SARS-CoV-2 replication, is reduced by about 3-fold by butyrate. Therefore, butyrate can control the replication of SARS-CoV-2 by down-regulating HMGB1 expression. Butyrate also prevents the invasion of SARS-CoV-2 by upregulating the major histocompatibility complex (MHC) class-II transactivator (CIITA) and CD74. Butyrate upregulates receptors of interleukin-1-β (IL-1β), interferon regulatory factor-7 (IRF7), and IFN-α/β in signal pathways activated by TLR at mRNA and protein levels to enhance innate immunity to viruses. Butyrate also down-regulates histone arginine demethylation Jmjd6 and chromatin remodeling complex members Smarca4 and Arid1a to inhibit SARS-CoV-2-induced cell death. In conclusion, butyrate can resist the infection of COVID-19 by down-regulation of genes necessary for SARS-CoV-2 infection and up-regulation of TLR and other antiviral pathways [125].

5.2. CAP and gut-lung axis

5.2.1. CAP can cause intestinal changes

The pathogens of CAP mainly involve bacteria, mycoplasma, chlamydia, and viruses. As far as bacterial pathogens are concerned, CAP is acquired through inhalation of bacterial pathogens from the autologous throat, apart from *Mycobacterium tuberculosis* and *Legionella*, which is able to be inhaled into the lung parenchyma through droplets, and *Pseudomonas*, which can be directly colonized in the trachea. The common bacterial pathogens of CAP in the clinic are *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Legionella*, *Klebsiella pneumoniae*, and *Moraxella catarrhalis*, etc. The viral pathogens of CAP include influenza A and B viruses, influenza type 1, 2, and 3, respiratory syncytial virus and adenovirus, etc. Other microbial pathogens include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Chlamydia psittaci*.

Pneumonia can cause disruption of symbiotic microorganisms in the gut. Intestinal microbial diversity (Shannon index) was reduced by 1.45 units ($P < 0.001$) in respiratory tract infection (RTI) patients in comparison with control samples, and the abundance of taxonomy was lower [126]. Pulmonary infection with a respiratory syncytial virus (RSV) and influenza virus causes significant changes in intestinal microbial diversity, in which the number of *Firmicutes* fell, and the number of *Bacteroides* grew [127]. Gut microorganisms α diversity was slightly lower in severe RSV disease patients. All RSV disease (moderate and severe) patients had considerably varied β diversity, compared with healthy infants, and microbial composition was significantly different among the three groups (healthy infants, moderate RSV disease, and severe RSV disease) [128]. An examination of intestinal microbial diversity in adults indicated the microorganisms ' alpha diversity in samples from individuals with recurrent respiratory infections (RRTI) was lower compared to normal controls. Classification analysis showed that the abundance of six phyla (*Firmicutes*, *Proteobacteria*, *Bacteroides*, *Actinobacteria*, *Verrucomicrobia*, *Tenericutes*) and four genera (*Enterococcus*, *Faecalibacterium*, *Bifidobacterium*, *Eubacterium*) had significant differences between the RRTI group and normal group. Additionally, in comparison to the normal group, the RRTI group had lower levels of *Eubacterium*, *Coprobacterium*, and *Bifidobacterium* while *Enterococcus* was more abundant [129]. In animal experimentation, mice infected with *Klebsiella pneumoniae* had considerably reduced concentrations of *Lactobacillus reuteri* and *Bifidobacterium pseudolongum*. A Spearman correlation analysis revealed a close relationship between variations in host metabolite concentrations and variations in the abundance and diversity of intestinal microorganisms. The concentrations of acetate, propionate, and butyrate in the intestinal tract and blood were lower in the infected group than in the control group. Supplementing the above SCFAs orally can reduce the vulnerability to infection with *Klebsiella pneumoniae*, characterized by a decreased bacterial burden in the lungs and increased survival [130]. Sencio et al.indicated sublethal influenza infecting temporarily altered the gut microbiome of mice, including its makeup and fermentation activities, manifested as a decrease in SCFA levels. Meanwhile, the decreased alveolar macrophage bactericidal activity is a result of less generation of the main SCFA acetate [131]. H7N9 infection will also alter the makeup of mice's gut microorganisms, primarily by suppressing the growth of the *Lachnocosterium* and *Rikenellaceae* gut group and encouraging the growth of *Akkermansia*, *Ruminococcus 1*, and *Ruminococcaceae_UCG_010*. Besides, H7N9 infection and *Akkermansia muciniphila* abundance were positively associated [132].

5.2.2. Mechanism of CAP affecting the intestinal tract

Mechanisms were explored through animal experiments. The reason for intestinal microbiota disturbance caused by pneumonia is mainly because of the immune system's activity during the course of pneumonia, which affects the gut through the CMIS. For example, influenza A virus (IAV) infection leads to increase cluster cell populations of epithelial cells in the small intestine, as well as ILC1 and ILC2. When cluster cells are absent, the increase in ILC2 is severely diminished, while ILC1 remained increased [133]. At the same time, IAV infection can remotely impair the intestinal barrier properties, causing impaired barrier performance and secondary intestinal infection, accompanied by reduced SCFA. Supplementing SCFA can partially offset this damage [134]. In addition, pneumonia may also be related to the trace element zinc, which is necessary for normal immune function. Research by Samuelson, D.R. indicated that pneumonia risk was raised by insufficient food consumption. The zinc transporter ZIP8 is crucial in the defense of the host, and ZIP8 deficiency can lead to intestinal dysregulation and decreased butyrate levels, impaired lung host defense, and worsening bacterial pneumonia [135].

5.2.3. Influence of intestinal symbiotic microorganisms on CAP

Numerous experiments on animals showed the significance of intestinal microorganisms in the host's resistance to infections caused by bacteria and viruses in the lungs. Intestinal microorganisms regulate the body's immune response mainly through the

microorganisms themselves and their secretions. After the IAV infection, the symbiotic microbes cause the appropriate activation of inflammatory bodies. Activation of inflammatory bodies leads to the transfer of DCs through lung tissue to the draining lymph nodes and activates virus specific CD4 and CD8T cells and triggers an immune response. Thus, regulating respiratory mucosal immunity [67]. Brown R.L. et al. have also found that intestinal microbes can trigger an increase in the production of GM-CSF in the lungs through IL-17A in response to infection and enhance respiratory defense [87]. CAP is most frequently caused by *Streptococcus pneumoniae*. When *Streptococcus pneumoniae* infects the lungs, Intestinal symbiotic SFB may suppress excessive inflammatory responses by promoting neutrophil breakdown, providing protection in immunocompromised hosts [136]. Another study found that the lack of innate defenses of hosts substances peptidoglycan recognition protein 4 (PGLYRP4), a known antimicrobial protein, would cause intestinal microbiota to change. This change improved the bacterial clearance rate of pulmonary infection caused by *Streptococcus pneumoniae*, boosted the immune cells' aggregation to the infected location, and enhances the bactericidal ability of phagocytes, and few mice suffer from bacteremia [137]. The gut microbiome is very tightly correlated with the severity of influenza. *Bifidobacterium animalis* has been proven to have an anti-influenza effect. When a fatal influenza infection occurs, the intestinal population of endogenous *Bifidobacterium animalis* can be expanded to strengthen the host's influenza defense, so as to alleviate the severity of influenza and reduce mortality [138].

SCFA produced by gut microbiota has been demonstrated to be significant in systemic immunity in patients with CAP. A transformation study involving cells and tissues from mouse and human lungs showed that intestinal microbiota and its SCFA were significant in the establishment and regulation of lung immunity. The metabolically active intestinal microbes (producing SCFA) can transport LPS and SCFA to the lungs, thus initiating the regulation of lung immune metabolism [139]. Animal experiments further reveal that oral supplementation with SCFAs from intestinal microorganisms can activate GPR43. SCFAs and GPR43 can up-regulate LAMTOR2, which promotes phagocyte-lysosomal fusion and phosphorylation of extracellular signal-regulated kinase (ERK) and increases the bacterial clearance ability of macrophages. SCFA promotes the clearance of *Klebsiella pneumoniae* by macrophages through the LAMTOR2-dependent signaling pathway [140]. Butyrate exerts a wide range of anti-inflammatory activities by activating signal pathways and inhibiting histone deacetylase, affecting the migration, adhesion, and cytokine expression of immune cells, along with cell proliferation, activation, and apoptosis. RSV-induced pneumonia is aggravated by dysregulation of the intestinal microbiome and disrupts cytokine regulation, manifesting that IFN-γ and IL-17 expression was upregulated, lung M1-like macrophage polarization was enhanced, and IL-5 expression was downregulated. *Clostridium butyricum* supplementation prevents inflammation aggravation and immunological responses that are out of balance, at the same time reverses the above reactions. In addition, in vitro and in vivo research confirmed that butyrate, a major metabolite generated by *Clostridium butyricum*, promotes M2 polarization of macrophages in RSV-infected intestinal microbiome dysregulation mice [141]. Acetate can also affect immune response. Acetate can improve the response of IFN-1 by activating membrane receptor GPR43, increasing the expression in the lung's interferon stimulating gene, and thus mediating the IFN-β reaction. This can reduce the viral load and pulmonary inflammation in mice infected by severe RSV, thus preventing RSV-induced diseases. IFN-1 is usually released after the virus identification and binds to interferon-alpha/beta receptor (IFNAR) 1 or 2, initiating signaling cascades involving JAK/STAT and inducing immune serum globulin (ISG) with direct antiviral activity [142]. The fecal transfer test also showed that IAV-conditioned microorganisms damaged the pulmonary defense against Pneumococcal infection through the change of acetate. Because the re-cloned mice treated with acetate reduced the bacterial load in the lungs [131]. Propionic acid has been shown to significantly modulate the pulmonary immune response in vitro and in vivo, and increased propionic acid generation in the gut microorganisms correlates with reduced lung inflammation [143]. besides, PSA from symbiotic *Bacteroides fragilis* activates $CD4^{+}$T cells through MHC II and then inhibits the progression of pulmonary inflammation in mouse models by expressing IL-10 [144].

6. Conclusion

The gut and lungs realize functional connections through the gut-lung axis channel composed of immune function and microbial interaction. Representatively reflects the close connection and interaction between various organs and tissues of humans as a whole, which is strong evidence of the human's holistic view. In our article, the mechanism of the gut-lung axis is briefly summarized and analyzed. The gut-lung axis is not only closely related to pneumonia, but also has important links with other pulmonary diseases, such as asthma, pulmonary hypertension, COPD, lung cancer, cystic fibrosis, and acute lung injury. It is not discussed in detail due to space limitations in this paper. The therapeutic effects of probiotics have also received high attention and recognition due to the significant association between the gut-lung axis and the lungs and intestines. Although the gut-lung axis theory was proposed earlier, there are still many gaps in the research, and there are still many hypotheses for the explanation of the mechanism. In the future, more research is required to determine the cross-talk pathway of the gut-lung axis and the exact efficacy of probiotics, in order to establish a novel treatment target for lung and even systemic diseases. At the same time, it provides a new idea and strong support for the overall concept of the human body.

Ethics approval and consent to participate

This article is a review, so there is no ethical approval or patient consent provided.

Consent for publication

This article has not been published before, and all authors agree to publication.

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Jing Guo: Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Le Wang:** Resources, Methodology, Data curation, Conceptualization. **Ningxin Han:** Software, Methodology, Investigation, Data curation, Conceptualization. **Caiyun Yuan:** Methodology, Formal analysis, Data curation, Conceptualization. **Yujie Yin:** Methodology, Investigation, Data curation, Conceptualization. **Tongxing Wang:** Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jiemeng Sun:** Validation, Software, Resources, Methodology. **Peipei Jin:** Visualization, Software, Resources, Methodology. **Yi Liu:** Visualization, Resources, Methodology, Investigation, Conceptualization. **Zhenhua Jia:** Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, 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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