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Perspective

Coronavirus disease 2019 and the gut–lung axis

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ABSTRACT

Gastrointestinal and respiratory tract diseases often occur together. There are many overlapping pathologies, leading to the concept of the 'gut–lung axis' in which stimulation on one side triggers a response on the other side. This axis appears to be implicated in infections involving severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which has triggered the global coronavirus disease 2019 (COVID-19) pandemic, in which respiratory symptoms of fever, cough and dyspnoea often occur together with gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhoea. Besides the gut–lung axis, it should be noted that the gut participates in numerous axes which may affect lung function, and consequently the severity of COVID-19, through several pathways. This article focuses on the latest evidence and the mechanisms that drive the operation of the gut–lung axis, and discusses the interaction between the gut–lung axis and its possible involvement in COVID-19 from the perspective of microbiota, microbiota metabolites, microbial dysbiosis, common mucosal immunity and angiotensin-converting enzyme II, raising hypotheses and providing methods to guide future research on this new disease and its treatments.

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Introduction

Turner-Warwick (1968) and Kraft et al. (1976) reported the first evidence of pulmonary–intestinal cross-talk nearly 50 years ago, when they noted the development of severe, chronic bronchopulmonary disease in patients diagnosed years previously with inflammatory bowel disease. Microbes seem to play an important role in this cross-talk by affecting normal and pathological immune responses in the gut and lungs (Budden et al., 2017; He et al., 2017; Enaud et al., 2020). For example, some studies have linked changes in the gut microbiome with changes in lung immunity (Olszak et al., 2012; Barfod et al., 2013; Russell et al., 2013; Chen et al., 2014). The lung microbiota also acts through the blood, and affects the gut microbiota (Sze et al., 2014). This communication between the gut and lungs has given rise to the concept of the 'gut–lung axis' (Marsland et al., 2015; Schuijt et al., 2016) – a feedback loop that can be stimulated from either side to induce a response on the other side (Dumas et al., 2018). In addition to microbes, microbiota metabolites and common mucosal immunity have also been studied extensively in the gut–lung axis (Figure 1). Gastrointestinal disorders (i.e. nausea, vomiting, abdominal pain and diarrhoea) (Guan et al., 2020; Huang et al., 2020; Wang et al., 2020) and respiratory tract disorders (i.e. fever, cough and dyspnoea) (Wang et al., 2020) often occur together in coronavirus disease 2019 (COVID-19) (Zhang et al., 2021), and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has not only been detected in oral swabs (Xu et al., 2020a; Zhang et al., 2020a), but also in anal/rectal swabs and stool specimens (Holshue et al., 2020; Tang et al., 2020; Xu et al., 2020b), which may indicate cross-talk between gut and lungs in COVID-19 (Ahlawat and Asha, 2020; Dhar and Mohanty, 2020; He et al., 2020; Allali et al., 2021).

The need to clarify whether the gut–lung axis contributes to COVID-19 is critical given studies suggesting that the presence of a gastrointestinal disorder in patients with COVID-19 may be related to a more aggressive clinical course, including acute respiratory distress syndrome, liver injury and shock (Jin et al., 2020; Luo et al., 2020). In addition, the risk factors for severity and mortality in COVID-19 (e.g. diabetes) are known to be associated with disorders of the intestinal flora (Singh et al., 2020). This is especially true for patients with metabolic syndrome such as high blood pressure, obesity and diabetes who exhibit severe viral infections, including respiratory infections (Badawi et al., 2018;

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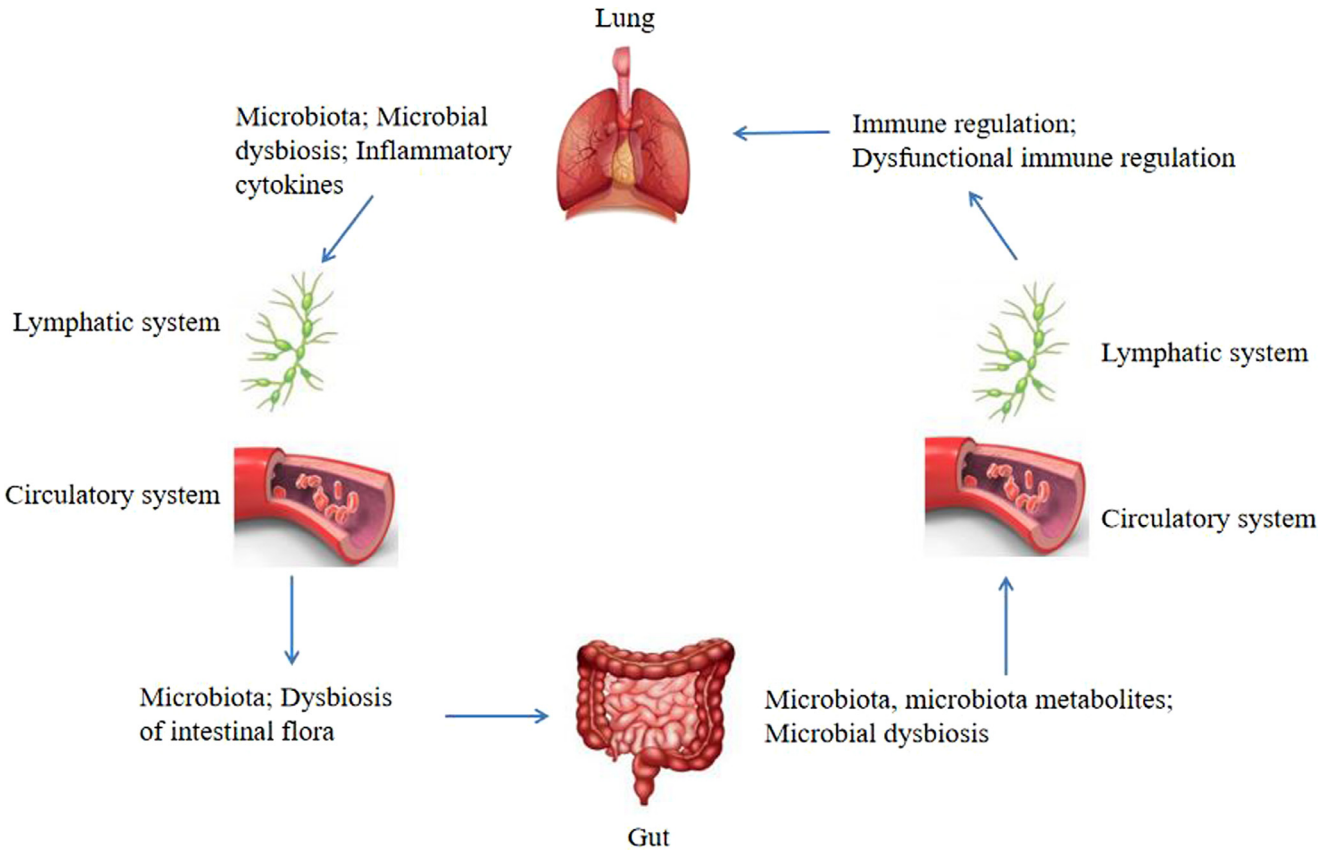


Figure 1. Bidirectional gut–lung axis. The gut microbiota and microbiota metabolites can regulate lung immunity through the lymphatic or circulatory systems, when the composition and diversity of the gut microbiota are changed, termed 'microbial dysbiosis'. Similarly, the lung microbiota may also affect the gut microbiota through the lymphatic or circulatory systems, and dysbiosis of the intestinal flora can be caused by lung microbial dysbiosis and inflammatory cytokines through the lymphatic or circulatory systems.

Honce and Schultz-Cherry, 2019). This raises the possibility that assessing activation of the gut–lung axis may be a way to stratify patients with COVID-19 by risk of severe disease, and that regulating this axis may be an effective treatment for COVID-19. As such, this article focuses on the latest evidence and the mechanisms that drive the operation of the gut–lung axis, and discusses the interaction between the gut–lung axis and its possible involvement in COVID-19 from the perspective of microbiota, microbiota metabolites, microbial dysbiosis, common mucosal immunity and angiotensin-converting enzyme II (ACE2), raising hypotheses and providing methods to guide future research on this new disease and its treatments.

The gut–lung axis

Gastrointestinal and respiratory tract diseases often occur together, and there are many overlapping pathologies (Roussos et al., 2003; Rutten et al., 2014), leading to the concept of the 'gut–lung axis' (Marsland et al., 2015; Schuijt et al., 2016; Budden et al., 2017). Indeed, the two tissues arise embryonically from the primitive foregut (Ramalho-Santos et al., 2000; Shu et al., 2007) and are similar in structure (Mestecky et al., 1978; Mestecky, 1987). Both tissues provide a physical barrier against microbial penetration and are colonized by the normal microbiota, thereby providing resistance to pathogens. These two tissues are extensively vascularized, and present a substantial epithelial surface area to the external environment (Takahashi and Kiyono, 1999; Labiris and Dolovich, 2003; Kuebler, 2005; Mason et al., 2008). In both cases, the epithelial surface is covered with the submucosa of loose connective tissue and mucosal-associated lymphoid tissue. This lymphoid tissue regulates antigen sampling, lymphocyte transport and mucosal defence (Holt, 1993; Forchielli and Walker, 2005). In this way, it can serve as the primary innate and adaptive immune response against invading pathogens (Tulic et al., 2016). Therefore, it is not surprising that these two sites interact in health and disease despite the different environments they face.

The gut–lung axis, microbiota and microbiota metabolites

There is a mutualistic relationship between the microbial community and the host. Microbes benefit from a stable, nutrient-rich micro-environment. In exchange, they have an essential role for the host, including the fermentation of dietary components to produce nutrients, vitamins and metabolites (Krajmalnik-Brown et al., 2012). A growing body of evidence supports the importance of constitutive sensing of micro-organisms and their metabolites in adjusting the immune system towards a healthy homeostasis (Maslowski et al., 2009; Samuelson et al., 2015).

The gut microbiota shares a mutually beneficial relationship with its host, where it produces various metabolites that can further signal to remote organs in the body through neural, endocrine, immune, humoral and metabolic pathways, regulating the body's metabolic homeostasis and organ physiology (Feng et al., 2018;Schroeder and Bäckhed, 2016). The complex interactions between the gut microbiota and the different organs result in the formation of the 'gut–organ axis', such as the gut–lung axis, gut–brain axis, gut–heart axis, gut–liver axis, gut–kidney axis, gut–liver–kidney axis etc. (Nicholson et al., 2012; Budden et al., 2017; Evenepoel et al., 2017; Tripathi et al., 2018; Cryan et al., 2019; Raj et al., 2020; Trøseid et al., 2020; Ahlawat and Asha, 2020).

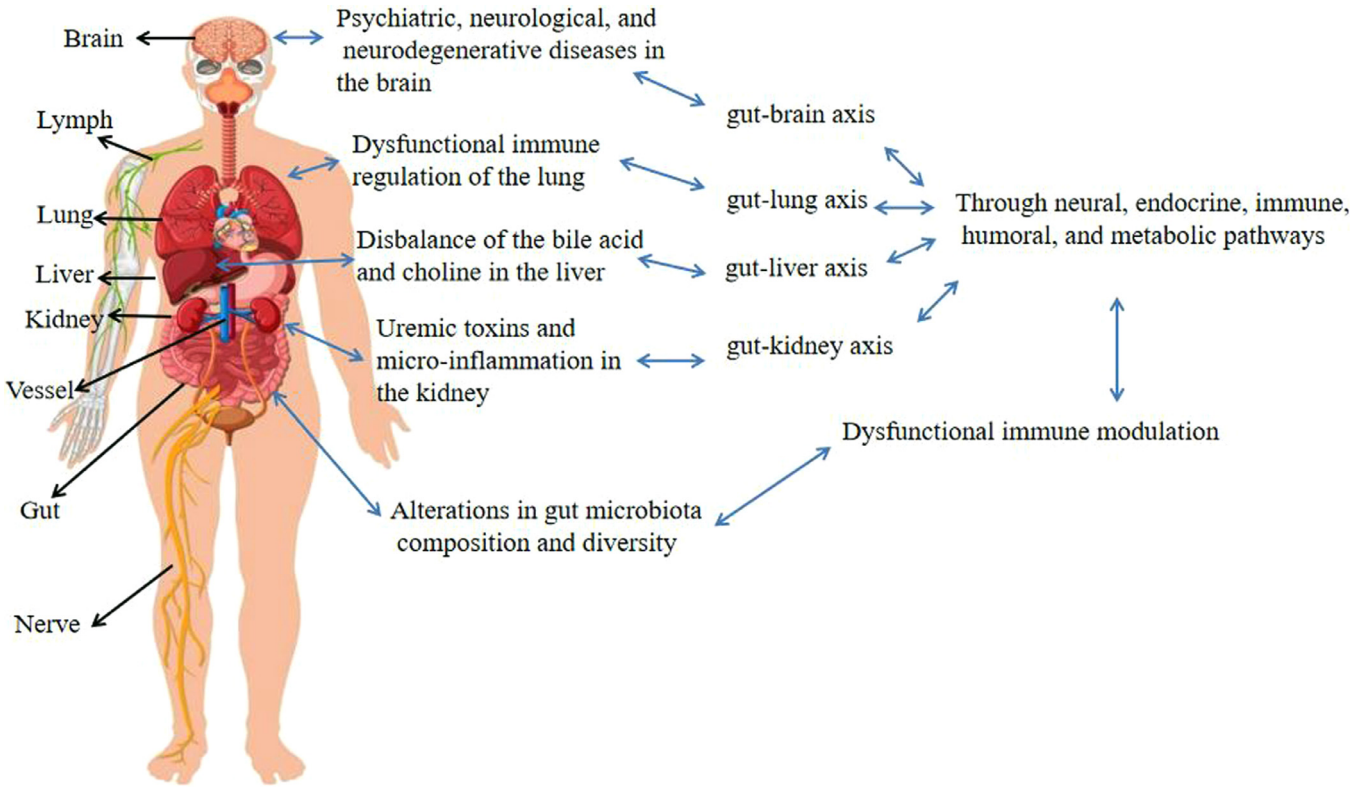


Figure 2. The gut–organ axis. The gut microbiota shares a mutually beneficial relationship with its host, where it produces various metabolites that can further signal to remote organs in the body through neural, endocrine, immune, humoral and metabolic pathways, regulating the body's metabolic homeostasis and organ physiology. Complex interactions between the gut microbiota and the different organs result in formation of the 'gut–organ axis', such as the gut–lung axis, gut–brain axis, gut–heart axis, gut–liver axis, gut–kidney axis, gut–liver–kidney axis etc. Within these axes, any alterations in gut microbiota composition and diversity may not only trigger gut disorders, but may also influence other organs and cause associated diseases.

Within these axes, any alterations in gut microbiota composition and diversity may not only trigger gut disorders, but also influence other organs and cause associated diseases (Figure 2). Thus, a better knowledge of gut microbiota and the 'gut–organ axis' will encourage the development of innovative diagnostic and therapeutic modalities for associated diseases.

The gut–lung axis is an important part of the 'gut–organ axis', and the influence of microbiota and its metabolites on the gut–lung axis has been reviewed recently (Trompette et al., 2014; Marsland et al., 2015; McAleer and Kolls, 2018) (Table 1). An example of the influence of microbiota on the gut–lung axis is that segmented filamentous bacteria in the gut can stimulate the lung T helper 17 response, protect it from *Streptococcus pneumoniae* infection, and enhance lung mucosal immunity (Gauguet et al., 2015). In murine studies, antibiotic-driven depletion of certain bacteria in the gut microbiome increases pulmonary viral infections (Ichinohe et al., 2011). Short-chain fatty acids (SCFAs) are the most widely studied metabolites, including butyrate, propionate and acetate, which have anti-inflammatory and immunomodulatory functions on lung homeostasis and immunity (Trompette et al., 2014; Koh et al., 2016). For example, SCFAs produced by *Bacteroidetes* spp. or *Clostridium* spp. can enhance influenza-specific CD8+ T-cell function and type I interferon (IFN) signalling in macrophages, thereby improving protection against influenza infection (Atarashi et al., 2013; Tanoue et al., 2016). Similarly, a high-fibre diet increased the relative abundance of SCFA-producing *Lachnospiraceae* spp. SCFA acetate protected mice from respiratory syncytial virus infection by producing IFN-β in lung epithelial cells through G-protein-coupled receptors (Antunes et al., 2019). In addition to SCFAs, another microbial metabolite that affects lung response is desaminotyrosine, which can protect mice against influenza virus infection by enhancing the type I IFN response (Steed et al., 2017). Taken together, these studies have proved the importance of symbiotic gut microbes and their metabolites in regulating lung homeostasis.

Table 1
Microbiota-derived metabolites modulating the gut–lung axis

Name of microbiota-derived metabolites	Mechanism of modulating the gut–lung axis	Ref.
SFB	Stimulate the lung TH17 response and protect it from *Streptococcus pneumoniae* infection, and enhance the lung mucosal immunity	Gauguet et al., 2015
SCFAs	Have anti-inflammatory and immunomodulatory functions on lung homeostasis and immunity	Trompette et al., 2014 Koh et al., 2016
	Enhance influenza-specific CD8+ T-cell function and type I IFN signalling in macrophages, thereby enhancing protection against influenza infection	Atarashi et al., 2013 Tanoue et al., 2016
	Protect mice from RSV infection by producing IFN-β in lung epithelial cells through G-protein-coupled receptors	Antunes et al., 2019
Desaminotyrosine	Protect mice against influenza virus infection by enhancing type I IFN response	Steed et al., 2017

SFB, segmented filamentous bacteria; SCFAs, short-chain fatty acids; TH17, T helper 17 cells; IFN, interferon; RSV, respiratory syncytial virus.

As discussed earlier, the presence of gastrointestinal disorders in patients with COVID-19 may be related to a more aggressive clinical course of disease (Jin et al., 2020; Luo et al., 2020), including acute respiratory distress syndrome, heart failure, renal failure, liver damage and even multi-organ dysfunction (Jothimani et al., 2020; Liu et al., 2020a; Mokhtari et al., 2020; Rabb, 2020; Zaim et al., 2020). As such, it should be noted that the gut–lung axis may not be the only axis involved in COVID-19; other axes may also be involved. Thus, the gut may affect lung function and consequently the severity of COVID-19 through several pathways. In COVID-19, upon attack of SARS-CoV-2, innate and adaptive immune system responses trigger inflammation and a cytokine storm in various organs such as the lungs, gut, heart, liver and kidneys, causing dysfunction of several organs (Jothimani et al., 2020; Liu et al., 2020b; Mokhtari et al., 2020; Rabb, 2020; Zaim et al., 2020). The gut dysfunction may change the composition and diversity of the gut microbiota (Aktas et al., 2020; Han et al., 2020; Xu et al., 2020a; Zuo et al., 2020). According to the 'gut–organ axis', any alterations in gut microbiota composition and diversity may not only trigger gut disorders, but also influence other organs such as the lungs, heart, liver and kidneys through neural, endocrine, immune, humoral and metabolic pathways, therefore explaining how the presence of gastrointestinal disorders in patients with COVID-19 may be related to a more aggressive clinical course of disease.

Consequently, in-depth understanding of the exact mechanism by which the gut and associated microbiota with derived metabolites interact with various organs in health and disease is crucial to counteract pandemics such as that caused by the ongoing SARS-CoV-2 infection.

The gut–lung axis and microbial dysbiosis

The human body is colonized by a variety of microbes, including bacteria, fungi, virus, archaea and protozoa (Eckburg et al., 2003; Grice and Segre, 2012; Debarbieux et al., 2017; Sender et al., 2016), most of which are found in the gastrointestinal tract (Shreiner et al., 2015). Healthy lungs were long considered to be sterile, but recent studies using culture-independent methods have shown that even healthy lungs harbour bacteria, viruses and fungi (Harris et al., 2007; Huang et al., 2010; Nguyen et al., 2015). These microbes seem to be important in nutrition, metabolism and defence against foreign pathogens (Sommer and Bäckhed, 2013), as well as epithelial homeostasis and ontogeny of innate and adaptive immunity (Gollwitzer and Marsland, 2015). Changes in the composition and activities of these microbes termed 'microbial dysbiosis or imbalance' can affect health in many ways, such as allowing opportunistic bacteria to grow, altering metabolic processes and immune responses, and triggering inflammation (Craven et al., 2012; Qin et al., 2012; Trompette et al., 2014). For example, dysbiosis of intestinal flora has been associated with respiratory diseases such as asthma (Dharmage et al., 2015; Ranucci et al., 2017) and cystic fibrosis (Bruzzese et al., 2014; Manor et al., 2016). A study has shown that endogenous *Bifidobacteria* spp. intestinal flora caused by fatal influenza infection can enhance resistance to the virus (Zhang et al., 2020b). Conversely, lung inflammation can affect the intestinal flora (Budden et al., 2017; Dumas et al., 2018; Dang and Marsland, 2019): influenza virus infection in mice can increase the number of Enterobacteriaceae and reduce the number of *Lactobacillus* spp. and *Lactococcus* spp. in the gut (Looft and Allen, 2012; Tirone et al., 2019), and after lipopolysaccharide is administered to mice, the dysbiosis of the lung microbiota will be accompanied by the disturbance of the intestinal flora due to the movement of bacteria from the lungs into the bloodstream (Sze et al., 2014). These studies have shown that microbes play an essential role in cross-talk between the gut and the lungs, and that microbial dysbiosis in the lungs may affect the homeostasis of the gut and vice versa. It is also possible that a continuum of microbiota lines the entire length of the mucosal membrane of the gut and lungs, and that the composition of the microbial communities changes throughout the mucosal compartments, so dysbiosis in one compartment may affect the stability of the other compartment.

Several studies have shown that microbial dysbiosis is significant in patients with COVID-19 (Aktas et al., 2020; Han et al., 2020; Xu et al., 2020b; Zuo et al., 2020). It has been shown that some patients with COVID-19 suffer from microbial dysbiosis, and the levels of *Lactobacillus* spp. and *Bifidobacteria* spp. are reduced (Xu et al., 2020a). Severe microbiota dysbiosis was also found in patients with COVID-19, including a large number of pathogenic bacteria, such as *Klebsiella oxytoca, Lactobacillus* spp., *Faecalibacterium prausnitzii* and tobacco mosaic virus (Han et al., 2020). In addition, the severity of the disease may be positively correlated with the abundance of *Clostridium hathewayi, Clostridium ramosum* and *Coprobacillus* spp., and negatively correlated with the abundance of *Faecalibacterium prausnitzii* (Zuo et al., 2020). The elderly are at greater risk of SARS-CoV-2 infection, and severe COVID-19 (Goyal et al., 2020; Lake, 2020) in this group may be because their intestinal flora is less diverse and contains a smaller population of beneficial micro-organisms such as *Bifidobacterium* spp. (Nagpal et al., 2018). These studies indicate the urgent need to restore the balance of microbiota in patients with COVID-19. There is scientific evidence to confirm the role of probiotics and prebiotics in restoring the gut/lung microbiota balance, and reducing the risk of secondary infection due to bacterial translocation (Kanauchi et al., 2018; Santacroce et al., 2019; Chan et al., 2020). All these considered, the use of probiotics and prebiotics in preventing COVID-19 is increasing in order to eliminate the virus and preclude disease progression to severe stages (Angurana and Bansal, 2020; Sundararaman et al., 2020; Bottari et al., 2021; Khaled, 2021; Santacroce et al., 2021). On the basis of the available evidence, the possible benefits of probiotic and prebiotic administration in COVID-19 may be through immunomodulatory actions on systemic inflammation or by indirect interaction with the lungs through the gut–lung axis. Although the immune benefits of probiotics and prebiotics are unquestionable, their potential roles against COVID-19 infection still warrant more clinical and laboratory investigations.

Further work is needed to clarify the apparent relationship between microbial dysbiosis and COVID-19. This work should examine whether dysbiosis is the cause or consequence of the disease, and whether prebiotics or probiotics can be used to reduce the burden and severity of this pandemic.

The gut–lung axis and common mucosal immunity

Mucosal tissues are located at the interface between the external world and internal tissues, so they act as the primary innate and adaptive defence against invading pathogens (Abt et al., 2012; Abrahamsson et al., 2014; Donaldson et al., 2016). Different mucosal parts in the body may act together as a system-wide organ to protect the host from foreign invaders (Gill et al., 2010; Wang and Tian., 2015). This concept of 'common mucosal immune system' was put forward by Bienenstock et al. (1978), who found that after adoptive transfer of donor-derived B cells into mice, B cells of mesenteric lymph nodes distributed in most mucosal tissues, while B cells of peripheral lymph nodes returned to their original peripheral positions. This concept may explain, for example, why vaccination in one mucosal site leads to protection in another mucosal site (Gallichan et al., 2001). Antigen exposure in the gastrointestinal tract can lead to the production of specific antibodies in the respiratory tract (Artenstein et al., 1997; Man et al., 2004; Kang and Kudsk, 2007).

Available evidence suggests that the gut and lungs are part of the common mucosal immune system. The system mainly comprises gut-associated lymphoid tissue (GALT) and bronchial-associated lymphoid tissue (BALT) (McGhee and Fujihashi, 2012). GALT, which is rich in innate and adaptive immune cells, makes a more significant contribution to mucosal immunity (Fagarasan and Honjo, 2003; Deitch et al., 2006). The blood and lymphatic vessels can transport these immune cells and factors from GALT to BALT (Qi et al., 2006; Samuelson et al., 2015), thereby providing and enhancing resistance to respiratory infections. In a mouse model, activated intestinal 2 group innate lymphoid cells were found in the lungs of mice injected with IL-25 in the gut (Huang et al., 2018). Therefore, lymph and blood can link the site of primary immunization in the gut to the site of action in the lungs. Whether or not immune cells and factors can be transferred from BALT to GALT through blood and lymph needs to be checked in future work.

Although the transfer of sensitized immune cells from GALT to BALT can enhance the immune response in the respiratory system, the over-reaction of patients with COVID-19 in the form of excessive inflammation can lead to acute lung injury, acute respiratory distress syndrome and multiple organ failure (Deitch et al., 2006; Senthil et al., 2006; Wang and Ma, 2008; Dickson et al., 2016; Channappanavar and Perlman, 2017; Mehta et al., 2020). It may also cause the intestinal mucus layer to be thin, reduce the surface area of the lumen, and impair the integrity of the intestinal barrier (Osband et al., 2004; Rupani et al., 2007; Ng and Tilg, 2020; Ong et al., 2020). Such damage will recruit more immune cells from the extra-intestinal space, exacerbating excessive inflammation and damage. These extra immune cells can then translocate from GALT to BALT, exacerbating excessive lung inflammation. This may explain why gastrointestinal symptoms are associated with more severe COVID-19 (Jin et al., 2020; Luo et al., 2020). Future research should examine whether these gastrointestinal symptoms are useful for identifying patients with COVID-19 at high risk of severe respiratory manifestations.

Immune cells express homing receptors that target them to certain tissues so that wherever they encounter antigens, they will subsequently migrate back to these tissues (Campbell and Butcher, 2002). This may contradict the idea that immune cells in the gut can be translocated to the lungs and affect the inflammatory response. One explanation for this apparent contradiction is that lung and gut tissues come from the same embryonic tissue to share similar homing receptors. Another explanation is that during an inflammatory response, especially an over-reaction, immune cells from one compartment can migrate to their target tissues and migrate to other tissues through interactions with surface molecules that the cells normally cannot recognize. For example, T effector memory cells activated in the gut during an inflammatory response may enter the systemic circulation and then interact with lung endothelial PNAd through L-selectin/CD62L, thereby causing them to trigger an inflammatory response in the lungs (Golubovskaya and Wu, 2016). Given the noticeable inflammatory changes in the gut and lungs during COVID-19 (Deitch et al., 2006; Channappanavar and Perlman, 2017; Ye et al., 2020), the homing and tissue targeting of immune cells may be altered in a way that supports a common mucosal immune response. Exploring these possibilities is an exciting and vital task for future research.

The gut–lung axis and ACE2

Angiotensin-converting enzyme II (ACE2) was first reported in 2000 by Tipnis et al. (2000) and Donoghue et al. (2000). It is a homologue of the classic enzyme ACE, but unlike ACE, it is a negative regulator of the renin–angiotensin system (RAS) (Verano-Braga et al., 2020). RAS has an intricate interlinked system that regulates physiological and pathological functions of the cardiovascular, renal and pulmonary systems, including dynamic control over systemic and local blood flow, blood pressure, natriuresis, and trophic responses to a wide range of stimuli (Iwai and Horiuchi, 2009). As a counter-regulator of RAS, ACE2 may be crucial for maintaining tissue homeostasis. In COVID-19, ACE2 has been identified as a functional receptor for SARS-CoV-2 pulmonary infection (Gheblawi et al., 2020). However, it should be noted that ACE2 is not only expressed on the surface of the lung alveolar epithelial cells, but also presents in most other tissues including heart, vessels, kidneys, brain and the gastrointestinal tract (Tipnis et al., 2000). The diverse functions and widespread distributions of ACE2 are critical to understanding of the varied clinical symptoms and outcomes of COVID-19.

In the gut, ACE2 physiologically regulates amino acid transport and has been related to gut immune and microbial homeostasis. Studies have shown that the lack of ACE2 in mice can damage the homeostasis of local tryptophan, change the intestinal microbiome, and make animals more susceptible to inflammation, leading to diffuse alveolar damage and a sharp increase in bacterial load in the caecum, as in acute lung injury (Hashimoto et al., 2012). It is reported that SARS-CoV-2 can downregulate the expression of ACE2 (Verdecchia et al., 2020), which may further limit the function of ACE2, impair the homeostasis of intestinal tryptophan, and cause gut dysbiosis, thereby affecting lung homeostasis through the gut–lung axis.

Perspectives and suggestions

This article describes the origin of the gut–lung axis and the latest progress in mediating, maintaining and regulating the gut–lung axis, and also investigates the potential involvement of the gut–lung axis in COVID-19 from the perspective of microbiota, microbiota metabolites, microbial dysbiosis, common mucosal immunity and ACE2. The following are some perspectives and suggestions that may guide future research on the mechanisms of COVID-19, and novel treatment and management strategies for COVID-19.

Firstly, microbiota and microbiota metabolites are necessary for immune homeostasis and may play an essential role in the gut–lung axis. Microbial dysbiosis may affect the homeostasis of the gut and lungs, which has also been reported in COVID-19. As probiotics and prebiotics can shape the intestinal flora to regulate the host's immunity significantly, it seems reasonable to employ probiotic and prebiotic treatment and specific strains of bacteria through faecal transplants to prevent and treat a bacterial or viral infection such as SARS-COV-2. Therefore, probiotics, prebiotics and faecal transplant treatment methods will be explored in COVID-19.

Secondly, according to the common mucosal immune system concept, different mucosal sites of the body function together as a system-wide organ to protect the host from foreign invading organisms. Like the gut–lung axis, an inflammatory response in the gut may be reflected in the lungs and vice versa. Therefore, any disease should not be treated separately because organs interact with each other through various methods. When it comes to COVID-19, it is not simply a disease of the lungs, but a disease that may affect the organs of the entire system. Targeting system-wide organs affected in COVID-19 may be a critical step in treating COVID-19 in the future.

Thirdly, ACE2 may play an essential role in COVID-19 through several aspects. It acts as a main route of invasion for SARS-CoV-2 because it is expressed on the surface of lung alveolar type II cells and upper oesophageal cells, stratified epithelial cells, and absorptive enterocytes in the ileum and colon. In addition, its expression in enterocytes can be used to regulate dietary amino acid uptake. It may be related to faecal–oral transmission. Thus, the containment of viral spreading and, more importantly, effects on immune and microbial homeostasis in the gut, may affect the lungs through the

gut–lung axis. Understanding the role of ACE2 in the gut–lung axis and COVID-19 is crucial for developing novel therapeutic strategies.

Last but not least, it is important to note that current understanding of the gut–lung axis has only just started to be deciphered, mainly based on epidemiological and clinical observations, and lack of basic research. In addition, to date, there is no direct evidence to support the notion that acting on the gut–lung axis may affect the course of SARS-CoV-2 infection. However, this remains a fascinating hypothesis due to the possible implications in clinical practice. Future work should combine basic research on the gut–lung axis and COVID-19 to clarify disease progression and how to treat or even prevent it.

Conclusion

Microbiota, microbiota metabolites and common mucosal immunity may play an essential role in mediating, maintaining and regulating the gut–lung axis, and the gut–lung axis may be involved in COVID-19. However, the exact mechanism between the gut–lung axis and COVID-19 is yet to be defined, needing further basic research and improved interventional experiments to elucidate the role of the gut–lung axis in COVID-19.

Declaration of Competing Interest

None declared.

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Ethical approval

Not required.

Author contributions

Dan Zhou and Hanmin Liu conceived the study, Dan Zhou and Qiu Wang wrote the manuscript, and Hanmin Liu and Qiu Wang revised the manuscript. All authors revised the manuscript and approved the submitted version.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.09.013.

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