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COVID-19 and the Microbiome: The Gut-Lung Connection

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Introduction

December 2019 marks the date of the first identified cluster of cases of viral pneumonia in Wuhan, China, later identified as a novel coronavirus. Shortly after, this novel coronavirus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease known as coronavirus disease 19 (COVID-19). This virus rapidly spread World-wide and on March 11, 2020, the outbreak was declared a pandemic by the World Health Organization (World Health Organization, 2021a). The rapid spread of SARS-CoV-2 is mediated by its high transmission rate, with aerosols being the main method of transmission (Anderson et al., 2020). Currently, angiotensin converting enzyme 2 (ACE2) has been identified as a functional receptor that SARS-CoV-2 binds with high affinity. Furthermore, ACE2, expressed in over 150 different cell types, plays a key role in regulating inflammatory and fibrotic pathways (Imai et al., 2005). Clinical manifestations of COVID-19 range from asymptomatic to severe viral pneumonia presenting with respiratory failure, multiorgan failure leading to sepsis and septic shock, and patient death (Huang et al., 2020). SARS-CoV-2 infection initiates a hyperinflammatory process, a cytokine storm, in which cytokine levels, such as interleukin 6 (IL-6), IL-10 and tumor necrosis factor α (TNFα) are significantly increased and may lead to multiorgan failure and death.

Additionally, emerging evidence highlights the importance of a complex interaction between enteric viruses, including coronaviruses, and other members of the microbiome (Bishop and Kirkwood, 2008). Gastrointestinal (GI) symptoms in COVID-19 patients, such as diarrhea, vomiting and abdominal pain, are frequently reported and point to dysbiosis in the gut microbiome. Recent advances are beginning to reveal the importance of the lung microbiome in overall human health. The lung microbiome has been linked to many respiratory diseases, including viral diseases such as influenza. Moreover, emerging evidence points to crosstalk that occurs between the respiratory and GI tract, which relies on their respective microbiota and is called the gut-lung axis. The gut-lung axis is bidirectional to allow for the passage of endotoxins, microbial metabolites, cytokines and chemokines. These components are released into the bloodstream thereby connecting the gut and lung microbiota (Dang and Marsland, 2019). Alterations in the gut microbiome alters immune responses and homeostasis in the airways and lung inflammation induces changes in the blood and gut microbiota. This article will focus on SARS-CoV-2 infection and its disease COVID-19, the microbiome composition in both the gut and lungs and their modulations during viral infection. Furthermore, we will review the gut-lung axis in health and during viral infection, and how a systemic cytokine storm compromises the health of COVID-19 patients.

COVID-19 Pathogenesis

Virology

Coronaviruses are a large family belonging to the *Coronaviridae* family in the *Nidovirales* order. The first coronavirus was identified in 1965 and has since become a large family (Tyrrell and Bynoe, 1966). The name "corona" stems from the crown-like spikes on the outer surface of the virus family that are visible under an electron microscope (Richman et al., 2014). The coronavirus family consists of viruses of zoonotic origin that infect humans, other mammals, and birds, and is characterized by single-stranded RNA as nucleic material within a nucleocapsid. The whole genome of SARS-CoV-2 was found to be 96% identical to the bat SARS-like coronavirus strain, Bat CoV RatG13, supporting the hypothesis that SARS-CoV-2 most likely emerged from bats (Paraskevis et al., 2020; Zhou et al., 2020). Malayan pangolins have been proposed as an intermediate host between bats and humans, again showing high similarities between the intermediate and human strain (Chams et al., 2020; Lam et al., 2020; Zheng, 2020). Coronaviruses are subcategorized into four genera (α, β, γ, and δ-coronaviruses), with the α- and β-coronavirus being of clinical importance for humans (Richman et al., 2014). SARS-CoV-2 was first isolated in the bronchoalveolar lavage fluid of COVID-19 patients in Wuhan, China. After genome sequencing and phylogenic analysis, SARS-CoV-2 was determined to be a member of the β-coronavirus group (Zhu et al., 2020). Genome-wide phylogenetic analysis specifies that SARS-CoV-2 shares 79.5% sequence identity with severe acute respiratory syndrome coronavirus (SARS) and 50% to Middle East respiratory coronavirus (MERS) (Lu et al., 2020). All three have been identified as highly pathogenic human coronaviruses. Among them, SARS was the first to be identified after being reported in China in 2002 (Zhong et al., 2003), while MERS was reported for the first time in Saudi Arabia in 2012 (Zaki et al., 2012). SARS and MERS have a case fatality rate (CFR) of 10% and 34.4%, respectively, while human-to-human transmission is limited, especially for MERS, due to its high CFR (Du et al., 2009; Wang et al., 2020b). Conversely, SARS-CoV-2 exceeds the transmission rates of both SARS and MERS, with to date, January 2021, nearly 100 million known cumulative cases (World Health Organization, 2021b). The estimated CFR of SARS-CoV-2 depends on the region, ranging from less than 0.1%–25% (World Health Organization, 2020). The receptor-binding domain (RBD) plays a crucial role for the infection of all three of these viruses, as it has been identified to mediate viral entry into the host cell. The RBD is part of a viral spike (S) protein and allows for binding to the host receptor. SARS and SARS-CoV-2 both recognize angiotensin converting enzyme 2 (ACE2) as its receptor (Kuba et al., 2005; Zhang et al., 2020c), while MERS recognizes dipeptidyl peptidase 4 as its receptor (Raj et al., 2013). However, evidence shows that SARS-CoV-2 binds to ACE2 at a significantly higher affinity than SARS (Tai et al., 2020; Zhang et al., 2020c). This may explain the high transmission rates of SARS-CoV-2 compared to SARS.

Epidemiology and Clinical Manifestation

The primary source of infection from human to human is currently due to viral shedding by COVID-19 patients, with severe patients being highly contagious. Asymptomatic patients also shed infectious viral particles during the incubation period (ranging from 2–14 days) and are a source of human transmission (Hu et al., 2020; Lauer et al., 2020). Respiratory droplets and contact transmission are the main routes of infection. Initial clinical features are much like those of influenza, including fatigue, fever, cough, sore throat and body aches. Additionally, patients may experience gastrointestinal (GI) symptoms, including diarrhea and vomiting (Huang et al., 2020). As disease severity progresses, common symptoms include shortness of breath and pneumonia, which may eventually lead to acute respiratory distress syndrome (ARDS). The elderly population and individuals with pre-existing medical conditions have the highest mortality rates from COVID-19. Indeed, pre-existing conditions or comorbidities, such as hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, and cerebrovascular disease, are indicated to be independent risk factors associated with COVID-19 patients (Wang et al., 2020a). The mortality rate of COVID-19 patients aged 60 years and over is much higher than that of patients under 60 years of age (Liu et al., 2020). This difference may be partially explained by the prevalence of (multi) comorbidities that occur in the elderly, as well as reduced immune function due to increased age (Niu et al., 2020). In severe COVID-19 cases, SARS-CoV-2 infection critically damages the airway epithelium, thereby activating severe and dysregulated immune responses. Histological examination from samples of COVID-19 patients with ARDS display hyperactive cytotoxic T-cells filled with large volumes of cytotoxic granules (Huang et al., 2020). In critically ill patients, including those suffering from ARDS, elevated IL-6 levels are found, which correlates to a hyperinflammation process called cytokine storm syndrome. IL-6 plays a primary role in sepsis, shock, respiratory failure, and multiorgan failure in these patients. Therefore, IL-6 associates with disease severity and prognosis (Coomes and Haghbayan, 2020). Moreover, reduced lymphocyte count or lymphopenia as a result of SARS-CoV-2 infection increases susceptibility of secondary infections (Huang et al., 2020). Consequently, SARS-CoV-2 infection triggers a cascade of immune responses and is influenced by multiorgan involvement.

Affected Health Areas

Clinical manifestations range widely between individuals suffering from COVID-19, and the involvement of various organs has been reported (Huang et al., 2020; Lauer et al., 2020; Pan et al., 2020). While the pathology has been widely studied in the lungs, studies on the mechanisms of multiorgan involvement are still in the early stages. SARS-CoV-2 infection causes a cytokine storm, which subsequently promotes systemic inflammation. In addition, multiorgan viral infection is hypothesized to be mediated through ACE2, followed by viral replication within infected cells that exponentially expands the number of infectious viral particles (Gan et al., 2020). ACE2 is expressed in many cell types, supporting its direct relationship with multiorgan involvement

(Hikmet et al., 2020). According to several studies, SARS-CoV-2 infection may be associated with inducing cardiac injury and increasing mortality rates in patients (Esakandari et al., 2020). Cardiovascular dysfunction includes myocarditis, heart failure, acute coronary syndrome, arrhythmias and myocardial inflammation caused by viral infection (Babapoor-farrokhran et al., 2020). Myocardial inflammation occurs in response to more than 20 different viral infections that may lead to ion channel dysfunction resulting in cardiac arrhythmias (Gaaloul et al., 2012). Due to particularly specific COVID-19 symptoms such as loss of smell, taste, vision or decrease of alertness, SARS-CoV-2 infection affects and may possibly promote brain and central nervous system (CNS) damage. Encephalitis has been reported in COVID-19 patients, and researchers found SARS-CoV-2 virus in the cerebrospinal fluid of these patients (Moriguchi et al., 2020). This suggests the virus crosses the blood-brain barrier. Furthermore, a recent murine study found that binding of the S1 protein of SARS-CoV-2 to ACE2 mediates viral entry into the brain (Rhea et al., 2020). To date, only a few studies have focused on COVID-19's damage to the brain and CNS and future studies are necessary to elucidate a better understanding of how this virus manifests neurological symptoms. Alternatively, renal symptoms in COVID-19 patients have been reported, and range from the presence of proteinuria and hematuria to acute kidney injury (AKI) (Hirsch et al., 2020). The exact mechanism behind COVID-19 associated AKI has yet to be unraveled, while theories propose that viral entry is mediated by ACE2. COVID-19 associated AKI is accompanied by the development of sepsis, multiorgan failure and may lead to septic shock and is therefore associated with high mortality rates (Nadim et al., 2020). SARS-CoV-2 infection of the gut and lungs, and the involvement of the microbiome will be discussed later in this chapter (see **The Gut, Lung and SARS-CoV-2** section).

Angiotensin Converting Enzyme 2

Angiotensin converting enzyme (ACE) and its homolog ACE2, are membrane-anchored glycoproteins, that both play a significant role in the renin-angiotensin-aldosterone system (RAAS) pathway. Angiotensin II is a key component for the RAAS pathway, in which it increases vasoconstriction, renal sodium reabsorption and potassium excretion, aldosterone synthesis, blood pressure elevation, and induction of inflammatory and pro-fibrotic pathways (Ferrario et al., 2005; Tikellis and Thomas, 2012). ACE is responsible for the production of angiotensin II, and ACE2 cleaves angiotensin II into angiotensin (1–7), which can then bind to the MAS-related G-protein coupled receptor. The MAS receptor has many beneficial actions upon activation, such as vasodilation, inhibition of cell growth, anti-thrombosis and anti-arrhythmogenic effects (Santos et al., 2018). Angiotensin (1–7) thereby counteracts the effects of angiotensin II, pointing to the importance of a well-balanced ACE/ACE2 ratio in the human body (Sanchis-Gomar et al., 2020). Imbalance of this ACE/ACE2 ratio is often caused by ACE2 downregulation, which may be the result of many factors including RAAS blockade (Hamming et al., 2007) and obesity (Bernardi et al., 2012). ACE2 is a functional receptor for both SARS and SARS-CoV-2 and plays a crucial role during infection. In the lungs, ACE2 reduces vascular permeability, thereby providing protection from acute lung failure (Imai et al., 2005) Additionally, ACE2 can be considered a digestion-related enzyme in human enterocytes, where it is a key regulator of dietary amino acid homeostasis, local innate immunity, expression of antimicrobial peptides (AMPs) and gut microbial ecology in the GI tract (Cole-Jeffrey et al., 2015). Interestingly, SARS-CoV-2 has also been shown to downregulate functional ACE2 by binding of its spike protein to ACE2 (Zheng et al., 2020). For more information an in-depth review on the role of ACE2 in COVID-19 pathophysiology was recently published (Bourgonje et al., 2020).

The Microbiome in the Gut and Lung and Its Role in the Gut-Lung Axis

The Gut Microbiota

The gut microbiome is one of the most complex ecosystems on Earth and is composed of many microorganisms, including bacteria, fungi, archaea and viruses. The composition of the gut microbiota is contingent on the intestinal site and the specific microenvironment, and also varies between individuals (Costello et al., 2009). Extensive research has been done to understand the importance of the microbiota in health and how it is altered during disease (Guinane and Cotter, 2013; Wang et al., 2017; Yamashiro, 2017; Young, 2012). The intestinal microbiome has many beneficial functions for the host. It contributes to the formation of intestinal architecture, metabolizes indigestible compounds thereby producing metabolites, supplies essential nutrients, such as vitamins, and defends against colonization by opportunistic pathogens (Yamashiro, 2017). Different alterations of gut microbiota, called gut dysbiosis, have been associated with various diseases and disorders, such as obesity, irritable bowel disease (IBD) and type 2 diabetes (T2D) (Walters et al., 2014; Yassour et al., 2016). Intestinal homeostasis depends on complex interactions between the microbiota, the intestinal epithelium and the host immune system, meanwhile the microbes gain habitat and nourishment from the host (Anand and Mande, 2018). The intestinal epithelium is composed of a single cell layer of intestinal epithelial cells (IECs). IECs form a barrier that separates the intestinal lumen from the lamina propria and one of the main function of IECs is to process and absorb dietary nutrients. Several other IECs functions include secretion of compounds to regulate microbial colonization, sensing of both beneficial and harmful microbes and generation and modulation of immune responses (Peterson and Artis, 2014). These different functions are carried out by highly specialized cells that are grouped together in IECs, such as enterocytes, Paneth and goblet cells (Kim and Ho, 2010). The intestinal epithelial lining is additionally covered by a thick mucus layer, which acts as a primary physical barrier from the lumen. Moreover, chemical barriers, including the acidic pH of the stomach and bile fluid, are the first defenses within the GI tract (Tennant et al., 2008). The mucosal barrier consists of mucins secreted by goblet cells, thereby physically inhibiting invasion by

intestinal microorganisms or toxins. Mucus secretion is regulated by the host sensing gut microbes and their metabolites, such as short chain fatty acids (SCFAs) and Th2 cytokines (Kim and Ho, 2010; Moro et al., 2010). SCFAs are produced by the fermentation of dietary fibers by SCFAs-producing bacteria (Louis and Flint, 2017). Butyrate, acetate and propionate are the most predominant SCFAs, and are important metabolites that maintain intestinal homeostasis (Venegas et al., 2019). Moreover, these SCFAs also regulate gene expression and cell proliferation (Lukovac et al., 2014; Park et al., 2016), promote the epithelial barrier by supporting the production of antimicrobial peptides (AMPs) by IECs (Zhao et al., 2018), and have immunomodulatory functions, such as anti-inflammatory effects (Li et al., 2018; Park et al., 2007). Anti-inflammatory cascades are activated by SCFAs binding to IEC cell surface G-protein coupled receptors (GPCRs) (Brown et al., 2003; Venegas et al., 2019). AMPs are produced by Paneth cells and are another important component in maintaining intestinal homeostasis. AMPs, part of the innate immune response, contribute to host defense against enteric pathogens and also have a homeostatic role in shaping the composition of the microbiota (Ostaff et al., 2013; Salzman et al., 2009). IECs express cell surface receptors named pattern-recognition receptors (PRRs), including Toll-like receptors (TLRs) and NOD-like receptors (NLRs), enabling them to recognize pathogen-associated molecular patterns (PAMPs) (Maloy and Powrie, 2011). PAMPs come in a wide variety stemming from viruses, bacteria, fungi, protozoa, and multicellular parasites. Upon sensing of PAMPs, such as lipopolysaccharides (LPS), the host gut response is activated and includes proliferation of gut epithelial cells, secretion of IgA into the gut lumen and expression of effector molecules, namely AMPs. The gut microbiome plays a key role in maintaining barrier integrity and in the development of host immunity. When gut dysbiosis occurs, this balance shifts and pathogenic bacteria form a majority, which leads to disease.

The Airway Microbiota

The lung microbiome entered a new era of discovery approximately a decade ago as researchers moved away from the hypothesis that the lung environment was "sterile" (Dickson et al., 2016a). Moreover, next-generation sequencing has allowed for major advances in our understanding of the respiratory microbiota and its potential functions (Cui et al., 2014; Morris et al., 2013). The bidirectional movement of air, in addition to the mucus layer within the respiratory tract, allows for the lung microbiome to be more dynamic and transient than the microbiome found within the GI tract (Dickson and Huffnagle, 2015; Huffnagle et al., 2017). While the lung microbiota has a low density of bacteria it harbors a wide variety of interacting microbiota that vary depending on location within the respiratory tract (Dickson et al., 2016a). The respiratory tract is divided into upper respiratory tract (URT) and lower respiratory tract (LRT) (**Fig. 1**). The URT consists of the anterior nares, nasal passages, paranasal sinuses, the nasopharynx and oropharynx, and the portion of the larynx above the vocal cords. The LRT includes the remaining portion of the larynx below the vocal cords, the trachea, smaller airways, such as bronchi and bronchiole, and alveoli (Weibel, 1963; Man et al., 2017). The large surface area of the airways is colonized by niche-specific bacterial communities at distinct anatomical sites. The composition of the lung microbiome depends on microbial immigration, elimination, and their relative growth rates. When these factors change, i.e., in disease, overgrowth of one species may occur causing a reduction of overall microbial diversity (Lemon et al., 2010; Morris et al., 2013). In healthy individuals, microbiome composition differs notably between the UTR and LTR (Watson et al., 2019). However, the existence of shared bacterial communities between lung and the oral cavity also occurs, suggesting bacteria enter the lung by direct mucosal dispersion and micro-aspiration (Bassis et al., 2015; Dickson et al., 2016a; Huxley et al., 1978; Morris et al., 2013). The most common genera shared between the lung and oral cavity are *Streptococcus* spp., *Prevotella* spp., and *Veillonella* spp. (Morris et al., 2013). The lungs predominantly have *Bacteroidetes* and *Firmicutes* while the oropharynx is dominated by *Firmicutes*, *Proteobacteria*, and *Bacteroidetes* (Dickson et al., 2016a; Lemon et al., 2010; Morris et al., 2013). Comparison of the LRT and URT microbiome identify only a few species that are not derived through dispersal from the URT, such as *Tropheryma whipplei* (Dickson et al., 2015; Morris et al., 2013; Segal et al., 2013). Interestingly, the nasal microbial community is found to be similar to skin microbiota, containing predominantly *Firmicutes* and *Actinobacteria* (Grice and Segre, 2011; Lemon et al., 2010; Tang Rasmussen et al., 2000).

Furthermore, the lung microbiome plays a major role in lung immunity and establishment of a well-balanced microbiome may be vital for fighting respiratory infections. The URT is a source of potential pathogens ready to multiply and subsequently spread toward the lungs. Additionally, the airway surface is in direct contact with the external milieu. Therefore, it is constantly exposed to invading microorganisms and several lines of defense are imperative to protect against potential infections (Lima et al., 2016; Schenck et al., 2016). A continuous layer of pulmonary epithelial cells, which are in close contact with immune cells, function as both a physical and biological barrier. Pulmonary epithelial cells express PRRs to recognize PAMPs, and additionally secrete a wide range of cytokines and chemokines (i.e., IL-6, IL-8, TNFα, MCP-1) (Leiva-Juárez et al., 2017; Whitsett and Alenghat, 2015). A mucus layer coats the pulmonary epithelial cells thereby protecting against infection by functioning as an initial physical barrier, much like that of the gut epithelium. Proteolytic enzymes, lysozymes expressed on the surface and in the fluids around the alveoli, and defense proteins, such as immunoglobulins, lactoferrin and defensins also play protective roles (Invernizzi et al., 2020). The lungs contain immune cells, such as dendritic cells, macrophages, lymphocytes (T-, B-, and NK cells), innate lymphoid cells and neutrophils, all of which support both innate and adaptive immune responses (Nicod, 2005). Lung resident memory $\gamma\delta$ T-cells stipulate a fast immune response at barrier surfaces, as they recognize previously encountered antigens through the lung mucosa. Moreover, $\gamma\delta$ T-cells play a role in cytokine and interferon production to help stop bacterial and viral infections (Cheng and Hu, 2017; Nicod, 2005). The formation of the airway microbiome occurs rapidly post-birth. Mice reach mature microbiome diversity within 2–3 weeks postnatally (Eva S. Gollwitzer et al., 2014) and humans over 2–3 months postnatally (Pattaroni et al., 2018). Importantly, the lung microbiome is required for normal alveolar development as Wostmann and colleagues reported germ-free

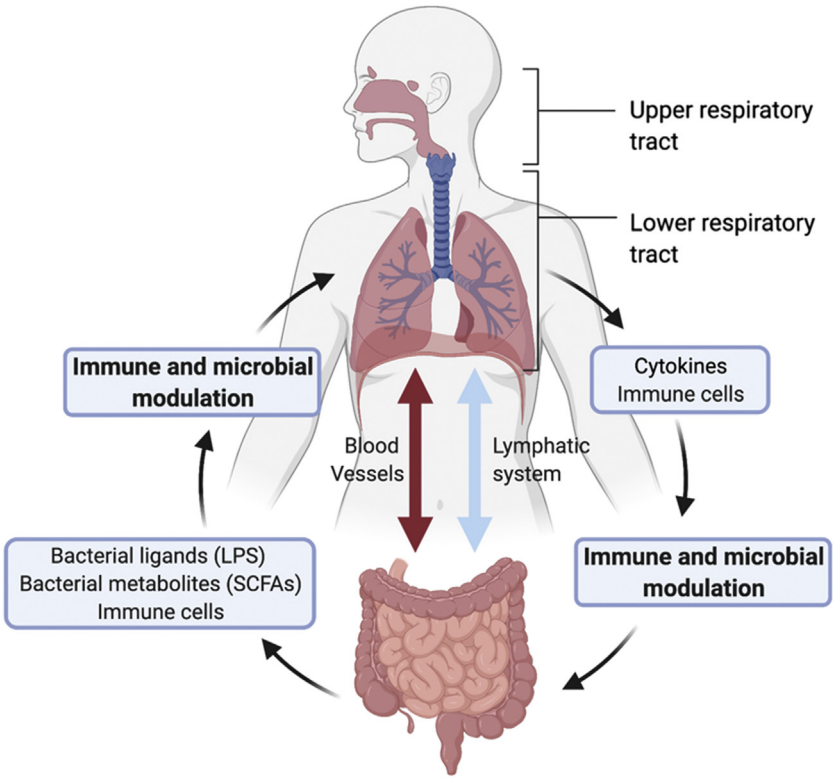

Fig. 1 Gut and Lung Axis. Microbiomes of the gut and lungs maintain bidirectional crosstalk. Bacterial ligands (lipopolysaccharides; LPS) and bacterial metabolites (short-chain fatty acids; SCFAs) from the gut enter the bloodstream and travel to the lung where they modulate immune responses and lung microbial composition. Gut intestinal epithelial cells interact with the microbiome to stimulate immune responses. The respiratory tract consists of an upper (UTR) and lower (LTR) respiratory tract (depicted by brackets), each of which is inhabited by unique niche-specific bacterial communities. The airway microbiota maintains lung homeostasis by acting on resident immune cells and regulating cytokine levels. Both immune cells and cytokines may enter the bloodstream and subsequently affect the gut microbiome. Source: Schematic was drawn using biorender (www.biorender.com).

rodents have smaller lungs (Wostmann, 1981), and Yun and colleagues demonstrated a decreased number of alveoli in germ-free mice (Yun et al., 2014). Interestingly, the latter study reported that reintroduction of the bacteria, *Lactobacillus* spp., normalized the number of mature alveoli (Yun et al., 2014).

Lung-Gut Crosstalk

Immune homeostasis is dependent on a well-balanced microbiome, including microbial components and metabolites that are important for maturation and priming of the immune system. The microbiome composition is affected by many environmental factors including diet, antibiotic treatment and even stress (Dong and Gupta, 2019). Emerging evidence points to a gut-lung axis, which allows for bidirectional crosstalk between gut microbiota and the lung microbiota. Altered gut microbiomes have been studied extensively and data suggest an association of altered microbiome with pulmonary diseases. For example, patients suffering from IBD or irritable bowel syndrome (IBS) have a higher prevalence of pulmonary disease (Keely et al., 2012; Lai et al., 2020; Wang et al., 2013a). Additionally, antibiotic use early in life increases the risk of developing asthma and atopy, which correlates with a reduced number of bacteria in the GI tract after antibiotic treatment (Korpela et al., 2016; Livanos et al., 2016; Noverr et al., 2005; Russell et al., 2015). Interestingly, gut microbiota play a protective role against viral and pulmonary infections (Schuijt et al., 2016; Yitbarek et al., 2018) due, in part, to its role in the regulation of the innate and adaptive immune responses (discussed in detail in **Promotion of Viral Infectivity by the Gut Microbiome** and **Suppression of Viral Infectivity by the Gut Microbiome** sections) (Keely et al., 2012). Conversely, other studies have focused on the impact of respiratory disease on the gut microbiome. Gut microbiome changes occur in many chronic lung disorders, including asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF) (Baral and Connett, 2008; Barcik et al., 2020; Roussos et al., 2003). A detailed review of gut microbiome changes during common respiratory diseases can be found elsewhere (Zhang et al., 2020a).

The gut microbiota is also involved in modulating the production of LPS and bacterial metabolites (SCFAs) and plays a key role in the migration of immune cells via the blood (**Fig. 1**) (Iwamura et al., 2017; Tada et al., 1996). Marsland and colleagues found that commensal-derived SCFAs enter the bloodstream and bone marrow to promote hematopoiesis (Trompette et al., 2014). This

group found that in cases of allergic airway diseases and respiratory diseases, gut derived SCFAs stimulate a protective mechanism by increasing macrophage and dendritic cell (DC) progenitors. Subsequently, the lungs were found to be populated by these DC progenitor cells where they matured and consequently activated Th2 effector cells, which then mediates the immune response through cytokine production (Dang and Marsland, 2019; Trompette et al., 2014). These findings suggest that SCFAs prime myeloid cells in the bone marrow, which after migration to the lungs may promote an anti-inflammatory environment. Although the underlying mechanism is not yet entirely understood, it is not surprising the two sites might have some form of crosstalk. The mature respiratory and GI tracts have their own distinctive environments and functions, yet both stem from the same embryonic origin and therefore have structural similarities.

Role of the Microbiome During Viral Infection

The Gut Microbiome and Viral Infection

Over the past decade it has become evident that the microbiome has a profound influence on the development of host immunity and susceptibility to infection and disease. Globally, the most common infections are caused by enteric viruses due to their ability to spread easily from one person to another. Enteric viruses replicate in tissues and mucosal surfaces and many are human pathogens (Bishop and Kirkwood, 2008). They encompass a wide variety of viruses that include gastroenteritis-causing viruses such as rotaviruses and adenoviruses, retroviruses, human immunodeficiency virus (HIV), noroviruses, polioviruses and coronaviruses, among many others (Bishop and Kirkwood, 2008). Viral replication and transmission are complex with a highly evolved relationship between the virus, microbiome, and the host. Recently, it has become clear that enteric viruses intimately interact with other members of the microbiome, which, in turn, affects their pathogenicity and infectivity. The complex and concurrent evolution of the many species of the microbiota has led to "transkingdom interactions" where microorganisms functionally regulate, and are regulated by enteric viruses (Li et al., 2019; Pfeiffer and Virgin, 2016). The microbiome may regulate viral infection by either promoting or suppressing viral infectivity. Conversely, enteric viruses may regulate the microbiome to increase their infectivity (Berger and Mainou, 2018; Karst, 2016; Li et al., 2019; Pfeiffer and Virgin, 2016) through a variety of mechanisms including facilitation of genetic recombination (Erickson et al., 2018), stimulation of lytic reactivation (Gorres et al., 2014), stimulation of viral attachment to permissive cells (Robinson and Pfeiffer, 2014), enhancement of viral stability (Kuss et al., 2011; Robinson and Pfeiffer, 2014), driving of target cell proliferation (Haga et al., 2016; Wilen et al., 2018), indirectly by modulating the immunoregulatory microenvironment (Kane et al., 2011), and suppressing local antiviral immune responses (Li et al., 2019). More in-depth recent reviews on the complex interactions between the commensal microbiome and enteric viruses can be found elsewhere (Karst, 2016; Li et al., 2019; Pfeiffer and Virgin, 2016).

Promotion of Viral Infectivity by the Gut Microbiome

Direct promotion of viral infectivity by the microbiome may occur through various cellular mechanisms. For example, the commensal microbiome may promote poliovirus infectivity by facilitating genetic recombination (Erickson et al., 2018). The Pfeiffer group demonstrated that pre-incubation of poliovirus with members of the gut microbiota prior to *in vitro* infection of HeLa cells leads to a higher chance of viral infection of two or more viruses and an increase in genetic recombination and mutation rate (Erickson et al., 2018). Poliovirus and reovirus have also been shown to be more environmentally and thermally stable in the presence of bacterial polysaccharides such as LPS and peptidoglycan. For example, antibiotic treatment prior to the introduction of poliovirus or reovirus significantly reduced viral infectivity and pathogenesis in mice (Kuss et al., 2011). Furthermore, poliovirus with reduced LPS-binding capacity displayed poorer environmental stability (Robinson and Pfeiffer, 2014). The lytic stage of viral infection is key to the success rate of viral propagation. Gorres and colleagues reported that SCFAs induce lytic reactivation of the Epstein-Barr virus and herpesvirus by inducing the synthesis of early antigens (Gorres et al., 2014). The microbiome also directly drives proliferation of viral target cells. For example, intestinal microbiome and type-2 cytokines promote expression and proliferation of gut Tuft cells (Lee et al., 2017). Tuft cells are a main reservoir of murine norovirus and human Tuft cells express a norovirus-specific CD300lf receptor (Haga et al., 2016; Lee et al., 2017). A higher amount of Tuft cells corresponds to increased levels of norovirus reservoirs and viral shedding (Wilen et al., 2018). Finally, by stimulating viral particle attachment to permissive cells, the microbiome allows for higher viral infectivity. For example, pretreatment of poliovirus with *Bacillus cereus* increases the infectivity of HeLa cells through the poliovirus receptor (PVR) by bacterial surface polysaccharides (Robinson and Pfeiffer, 2014).

Transkingdom interactions may also indirectly enhance viral infectivity by altering the immune environment and suppressing local antiviral immune responses (Karst, 2016). More specifically, viruses may suppress humoral and adaptive immune responses by exploiting the commensal microbiome's indispensable role in the development and fine-tuning of the host immune system (Lee and Mazmanian, 2008; Shi et al., 2017; Zheng et al., 2020). The intestinal microenvironment has evolved to maintain homeostasis between the host and commensal microbiome. Antigen sensing and recognition of commensal microbes leads to cytokine secretion and regulatory T cell (Treg) activation and proliferation to maintain immunological tolerance (Palm et al., 2015; Pezoldt et al., 2018; Strowig et al., 2018). By interacting directly with commensal bacteria, viruses may evade detection and exploit bacterial immunotolerance to promote infectivity and transmission. For example, using germ-free and antibiotic-treated mice, Kane and colleagues demonstrated that mouse mammary tumor virus (MMTV), which is normally transmitted to offspring through the mother's milk, could not be transmitted in the absence of the gut microbiome (Kane et al., 2011). They observed that MMTV utilizes bacteria-derived LPS to induce the production of Treg immunoregulatory cytokine IL-10, thereby evading adaptive immune

responses and maintaining persistent infectivity (Kane et al., 2011). Similarly, infection of IL-10 deficient mice with norovirus, an otherwise mildly inflammatory infection, induced extreme intestinal inflammation. This effect was absent in germ-free IL-10 deficient mice, and re-introduction of a functional microbiome induced intestinal inflammation (Basic et al., 2014). Enteric viruses also suppress local antiviral immune responses such as antibody production and interferon (IFN) signaling (Karst, 2016). Germ-free mice have a higher antiviral antibody response compared with control mice in response to rotavirus infection, including higher fecal IgA, serum IgA and serum IgG (Uchiyama et al., 2014). Baldridge and colleagues found that antibiotic-treated mice produced less antiviral serum IgA up to 35 days post-norovirus infection (Baldridge et al., 2015). By using various strains of mice treated with antibiotics, they found that mice lacking type III interferon receptor (IFNλ), signal transducer and activator of transcription 1 (STAT1) or interferon-regulatory factor 3 (IRF3), could all be infected with norovirus regardless of the commensal microbiome (Baldridge et al., 2015). This group later identified IFNλ, also called type III IFN, to control and prevent persistent murine norovirus infection (Nice et al., 2015).

Suppression of Viral Infectivity by the Gut Microbiome

As discussed above, the gut microbiome is vital for the development and maintenance of a healthy host immune response. Due to its importance in maintaining intestinal homeostasis, it has been hypothesized that the microbiome may be of importance in the defense against viral pathogens. Several studies established a vital role for the microbiome in suppressing viral infection by demonstrating direct suppressive mechanisms that include the adsorptive trapping of viruses, suppression of viral replication, blocking of cell internalization processes and the destabilization of viral morphology (Domínguez-Díaz et al., 2019; Li et al., 2019). For example, *Enterococcus faecium* directly prevents influenza infection by adsorptive trapping of the virus (Wang et al., 2013). Moreover, some commensal species may directly destabilize influenza morphology and infectivity through LPS (Bandoro and Runstadler, 2017). Finally, Botić and colleagues found that commensal lactic bacteria directly bind to vesicular stomatitis virus thereby effectively reducing its infectivity (Botić et al., 2007).

In addition to direct mechanisms, the microbiome may indirectly suppress viral infection by enhancing antiviral immunity (Li et al., 2019). Indeed, using a genome-wide transcriptomic approach, Artis and colleagues demonstrated that broad-spectrum antibiotic treated mice have diminished innate and adaptive antiviral immune responses and significantly delayed viral clearance indicating a key role for the microbiome in suppressing viral infection (Abt et al., 2012). Bacterial flagellin inhibit rotavirus infection by the activation of pattern-recognition receptors (PRRs) and subsequent release of IL-18 and IL-22 (Zhang et al., 2014). Murine norovirus replication may also be blocked by the *Lactobacillus* genus *in vitro,* and treatment with retinoic acid increases the antiviral effects of vitamin A *in vivo*, which may be mediated by *Lactobacillus*-mediated IFN production (Domínguez-Díaz et al., 2019; Lee and Ko, 2016). *Clostridium orbiscindens*, a gut commensal, may enhance type I IFN signaling to promote immune protection against influenza infection (Steed et al., 2017). Toll-like receptors (TLR) may also have a role in establishing antiviral immunity through the microbiome. TLR2 activation via the commensal microbiome during viral infection is vital in the recruitment of innate immune cells, specifically mast cells, which release the antiviral protein cathelicidin (Wang et al., 2012). Gonzalez-Perez and colleagues demonstrated that TLR ligand stimulation by the microbiome is critical in restoring IFN-γ responses, $CD8^+$ T cell responses and reduced mortality from viral infection in antibiotic-treated mice (Gonzalez-Perez and Lamousé-Smith, 2017). Overall, these studies demonstrate that the microbiome plays an important part in suppressing viral infection via direct and indirect mechanisms.

The Lung Microbiome and Viral Infection

Recent advances have been made in elucidating the role of the lung microbiome in the context of viral infections (Enaud et al., 2020; Hanada et al., 2018). Similar to the intestinal microbiome, commensal microbes of the upper and lower respiratory tracts are crucial for the development and maintenance of local immunological homeostasis and in promoting tolerance of commensal species (Hanada et al., 2018). Primarily consisting of the major phyla Bacteroidetes and Firmicutes, the lung microbiome includes *Prevotella*, *Veillonella* and *Streptococcus* species (Dickson et al., 2015; Morris et al., 2013). These species provide bacterial colonization of the respiratory tract that induces local immune cell maturation and initiates commensal immunotolerance through PD-L1 (Eva S Gollwitzer et al., 2014). The absence of microbial lung colonization in mice promotes higher pulmonary Th2-induced cytokine and IgE production leading to allergic airway inflammation (Herbst et al., 2011). The commensal lung microbiome contributes to the establishment of resident memory B cells, which are important in the defense against pulmonary viral infections such as influenza (Allie et al., 2019). *Staphylococcus epidermidis*, an URT commensal bacterium, directly blocks influenza replication and further infection via the production of Embp, a large extracellular matrix-binding protein (Chen et al., 2016). Evidence points to microbial dysbiosis within the URT caused by respiratory infections, thereby priming the URT for bacterial secondary infections (Bogaert et al., 2004). Furthermore, in animal models influenza infection increases the amount of pathogenic bacterial colonization in the URT, increasing the risk for secondary bacterial infections (Peltola et al., 2006; Tong et al., 2000). This finding is substantiated in patients as one study determined that children infected with influenza have a 15-fold increase in nasopharyngeal titers of *Streptococcus pneumoniae* (Vu et al., 2011).

Crosstalk Between Gut and Lung During Viral Infection

Gut microbiota may also have distal protective effects and play a role in the defense against respiratory viral infection (Domínguez-Díaz et al., 2019; Ichinohe et al, 2009, 2011). In addition to regulating local intestinal immunity, the commensal gut microbiome is vital in providing distal immunity through its stimulation of immune cells that then migrate to other organs (Belkaid and Hand, 2014). For

example, broad-spectrum antibiotic treatment, which disrupts gut microbiome composition, leads to reduced B and T cell responses to influenza in the lung (Ichinohe et al., 2011). Moreover, Ichinohe and colleagues demonstrated that inflammasome-mediated dendritic cell migration stimulates a T cell influenza-specific response in the lung and that antibiotic treatment decreased beneficial gut commensals and abrogated that effect (Ichinohe et al., 2011). The gut microbiome may also regulate influenza-specific immune responses through IgA secretion, activation of Th1 cells and an upregulation of TLR7 signaling in the lung (Ichinohe et al., 2011; Wu et al., 2013). Belkacem and colleagues demonstrated that bacterial species *Lactobacillus paracasei* and *Lactobacillus plantarum* may suppress the inflammatory response to influenza in the lung by releasing the immunoregulatory cytokine IL-10 (Belkacem et al., 2017). Gut microbial products may also play an important role in distally regulating viral infectivity in the lung. Short chain fatty acids are required for intestinal health and immunity and may have an important role in fighting against viral infection in the lungs (Anand and Mande, 2018; Den Besten et al., 2013; Venegas et al., 2019). Gut-derived SCFAs traverse the intestinal barrier and distally act as signaling molecules in the lungs by suppressing inflammatory and allergic responses (Anand and Mande, 2018; Cait et al., 2018). In a mouse model of asthma, SCFAs receptor-deficient mice had increased inflammatory responses (Trompette et al., 2014). Recently, Trottein and colleagues demonstrated that influenza infection alters SCFAs production by the gut microbiome, which increases the likelihood of secondary bacterial infection in the lung post-influenza (Sencio et al., 2020). Additionally, decreased production of the SCFA acetate in the gut reduces bactericidal activity of alveolar macrophages. Supplementation with acetate restored alveolar macrophage activity via the SCFAs receptor FFAR2 and reduced the likelihood of bacterial infection in the lung (Sencio et al., 2020). Moreover, weight loss due to respiratory syncytial virus (RSV) or influenza infection leads to altered gut microbiota compositions and fecal metabolomes, including SCFAs production (Groves et al., 2019). Allogeneic hematopoietic stem cell transplantation patients with significantly higher amounts of butyrate-producing bacteria in the gut were five-fold less likely to develop lower respiratory tract viral infections following stem cell transplantation (Haak et al., 2018). These studies point to crosstalk mechanisms between gut and lung microbiomes that are crucial for the role of the microbiome and its metabolites in the defense against distal viral infection.

Modulation of the Commensal Microbiome by Viral Infection

Disturbances of the commensal microbiome have been implicated in a range of pathologies including IBD, asthma, sepsis and cancer (Fay et al., 2017; Matsuoka and Kanai, 2015; Zeng et al., 2017; Zheng et al., 2020). Over the past decade, it has become clear that the host and microbiome are in homeostasis and this relationship is crucial in the maintenance of human health (McDonald et al., 2016; Shi et al., 2017). Moreover, viral infection by HIV, influenza, hepatitis B (HBV) and C (HCV) or norovirus negatively affects the microbiota and leads to dysbiosis thereby inducing unfavorable health outcomes (Li et al., 2019). For example, marked increases in pathogenic bacterial species as well as consistently reduced microbiota richness were observed in HIV-infected patients (Noguera-Julian et al., 2016; Vujkovic-Cvijin et al., 2013). These effects may be, in part, due to the immunosuppressive nature of HIV infection via a depletion of Th17 cells (Manfredi and Chiodo, 1999). Influenza viruses significantly alter the composition of healthy microbes in the URT, the primary site of infection. Using next-generation 16S rRNA sequencing, Edouard and colleagues found an enrichment in potentially pathogenic species including *Staphylococcus aureus, Corynebacterium propinquum/pseudodiphtheriticum* and *Haemophilus influenzae*, and a decrease in members of the core microbiota *Prevotella* spp. and anaerobes (Edouard et al., 2018). Changes in the gut microbiome upon influenza infection have also been observed, albeit with contradicting results. Although increased, unchanged and decreased levels of *Bacteroidetes* have been found in influenza-infected mice, a consistent decrease in *Firmicutes* was identified in each of those studies (Groves et al., 2018; Wang et al., 2014; Yildiz et al., 2018). Dysregulation of the immune system by influenza infection is, in part, a major contributor to microbial dysbiosis. It causes an increased production of type I IFN in the lung leading to a decrease in *Proteobacteria* and obligate anaerobes, and an overproduction of IFN-γ by lung derived $CD4^+$ T cells in the gut that promotes an abnormal Th17 response and subsequent intestinal immune injury (Deriu et al., 2016; Wang et al., 2014).

The Gut, Lung and SARS-CoV-2

Early on in the pandemic it became evident that elderly patients suffering from SARS-CoV-2 infection had worse prognoses and outcomes (Shahid et al., 2020). It has been established that aging alters the gut microbiome composition with a lower abundance of probiotic strains, such as *Bifidobacteria*, and a reduced number of species producing butyrate (Salazar et al., 2019). This hints to the importance of a healthy microbiome in fighting SARS-CoV-2 infection. SARS-CoV-2 invades host cells, thereby activating a series of immune responses. Viral RNA and PAMPs can be detected by PPRs in the cell and serve as primary viral sensors. This recognition activates a downstream signaling cascade to activate the innate immune response and the development of adaptive immune response (Leiva-Juárez et al., 2017). The mechanism of SARS-CoV-2 infection whereby immune responses are altered is similar to the more studied SARS and MERS-CoV infections (Prompetchara et al., 2020). Macrophages are directly affected by these three viruses, causing an upregulation of numerous pro-inflammatory cytokines, including TNFα and IL-6 (İnandıklıoğlu and Akkoc, 2020).

COVID-19 and the Intestinal Tract

While COVID-19 patients commonly present with a fever and respiratory disease, some patients also experience GI symptoms, such as vomiting, diarrhea and abdominal pain (Huang et al., 2020). COVID-19 patients may have GI impairments prior to the appearance of

respiratory conditions (Kotfis and Skonieczna-Żydecka, 2020). Notably, GI symptoms are increasingly reported as common symptoms in COVID-19 patients. Ghimire and colleagues reported in a systematic review and meta-analysis that 15.74% of total hospitalized COVID-19 patients experienced at least one GI symptom, with diarrhea being the most prevalent (Ghimire et al., 2021). Diarrhea is also associated with increased severity of the disease and worse prognosis (Ferreira et al., 2021; Ghimire et al., 2021). Interestingly, alterations in fecal microbiome composition as well as fecal viral RNA shedding was observed in hospitalized patients (Wang et al., 2020c; Zuo et al., 2020). These microbial alterations are characterized by a decrease in bacterial diversity, with a shift toward pathogenic bacteria and away from beneficial symbionts (Gu et al., 2020; Shen et al., 2020a). The loss of beneficial symbionts correlates with reduced SCFAs production. Butyrate is a histone deacetylase inhibitor that maintains acetylation of histones, affecting chromatin organization and gene expression. Butyrate helps maintain intestinal barrier integrity as well as AMP production, cell proliferation and decreases inflammation (Anand and Mande, 2018; Peng et al., 2009). Emerging evidence suggests that butyrate may control SARS-CoV-2 replication (Li et al., 2021), thereby playing a key role during infection. Shen and colleagues identified molecular changes in sera from severe COVID-19 patients, as well as characteristic protein and metabolite changes such as a decrease of SCFAs (Shen et al., 2020a). The Clevers group reported that the intestinal epithelium supports SARS-CoV-2 replication, in which enterocytes produce viral particles after infection. In their study, human small intestinal organoids (hSIOs) were used to demonstrate and confirm SARS-CoV-2 infection of enterocytes (Lamers et al., 2020). Viral replication in the intestine exponentially increases the viral load within the digestive mucosa (Infusino et al., 2020). Dendritic cells are attracted to the site of infection and activate immune responses through macrophages, B- and T-cells. Activated immune cells upregulate TNFα, IFNγ and IL-6 cytokine production (Moore and June, 2020). High levels of IL-6, in turn, stimulate increased secretion of vascular endothelial growth factor (VEGF), IL-8, and even more IL-6 and decrease E-cadherin expression (Tanaka et al., 2016). Upregulated VEGF and reduced E-cadherin levels then promote increased vascular permeability and loss of intestinal barrier integrity (Dejana et al., 2008). Furthermore, Zhang and colleagues have described the enteric symptom of diarrhea to be connected with ACE2 expressing enterocytes (Zhang et al., 2020b). SARS-CoV-2 enters cells by binding to ACE2 resulting in impaired ACE2 function. Altered ACE2 activity negatively affects dietary amino acid homeostasis, local innate immunity, expression of antimicrobial peptides and gut microbial ecology in the GI tract (Ahlawat et al., 2020; Cole-Jeffrey et al., 2015). The gut dysbiosis and (partial) loss of ACE2 function result in a leaky gut. The loss of a well-balanced microbiome negatively impacts the generation and modulation of immune responses, which further compromises the host's immune response to SARS-CoV-2 infection and potential comorbidities (Viana et al., 2020) (**Fig. 2**).

COVID-19 and the Lungs

SARS-CoV-2 is primarily transmitted through aerosols, thereby naturally entering the respiratory tract. Once in the respiratory tract, SARS-CoV-2 may infect epithelial cells expressing ACE2. Upon infection, the replication and release of the virus causes pyroptosis, a highly inflammatory form of lytic-programmed cell death. Pyroptosis is characterized by release of damage-associated molecular patterns (DAMPs), which, in turn, are recognized by neighboring epithelial cells, endothelial cells and alveolar macrophages (Fink and Cookson, 2005). Subsequently, proinflammatory cytokines and chemokines, including IL-6, IL-10, macrophage inflammatory protein 1α (MIP1α), MIP1β and MCP1, are released. These proteins attract immune cells (monocytes, macrophages, and T-cells) to the site of infection, promoting further inflammation (Tay et al., 2020). In severe COVID-19 cases, a defective immune response may lead to accumulation of immune cells in the lung, causing upregulated pro-inflammatory cytokine production (Channappanavar and Perlman, 2017). Furthermore, SARS-CoV-2 may infect lung epithelial stem cells, severely affecting the regeneration of the lung epithelium (Valyaeva et al., 2020). Pyroptosis and the lack of epithelial cell regeneration impairs the barrier function of the epithelial lining, allowing for fluid leakage into lung alveoli (**Fig. 2**). Notably, severe cases of COVID-19 share a common complication, namely ARDS (Huang et al., 2020). ARDS is the result of damage to the lung epithelium that promotes a fluid buildup within alveoli, thereby decreasing blood oxygen levels (Diamond et al., 2020). A recent study has shown that ARDS caused by COVID-19 and ARDS from different etiologies have only small physiological differences (Grieco et al., 2020). Previous studies found an abundant presence of gut-specific bacteria, such as *Bacteroides* spp., in the bronchoalveolar lavage fluid from individuals with ARDS. In these individuals alveolar TNFα levels significantly correlate with altered lung microbiome (Dickson et al., 2016b). The change in microbiota in ARDS patients is associated with increased serum cytokine IL-6 (Kyo et al., 2019). Moreover, lung microbiome composition predicts a poor prognosis and death in severely ill ARDS patients (Dickson et al., 2020). To date, two studies have analyzed the lung microbiome from COVID-19 patients. Shen and colleagues sampled bronchoalveolar lavage fluid from COVID-19 patients ($n = 8$), community-acquired pneumonia ($n = 25$), and healthy controls ($n = 20$) and a significant difference was found for both diseased states compared with controls (Shen et al., 2020b). In this study a shift toward pathogenic microbes was observed in COVID-19 patients bronchoalveolar lavage fluid indicating gut microbial dysbiosis. In the second study, deceased COVID-19 patients ($n = 20$) were subjected to microbial biopsies and increases in both bacterial and fungal species were found (Fan et al., 2020). Larger sampling sizes and future studies are needed to accurately determine how COVID-19 impacts the lung microbiome.

COVID-19 and the Gut-Lung Axis

Lung-gut crosstalk occurs in respiratory diseases (see **Lung-Gut Crosstalk** section) The importance of this bidirectional interaction between gut and lung may be important during SARS-CoV-2 infection, although studies remain limited at this time. Early on in the pandemic, an association was identified between gut microbiota dysbiosis and poor outcomes of elderly COVID-19 patients.

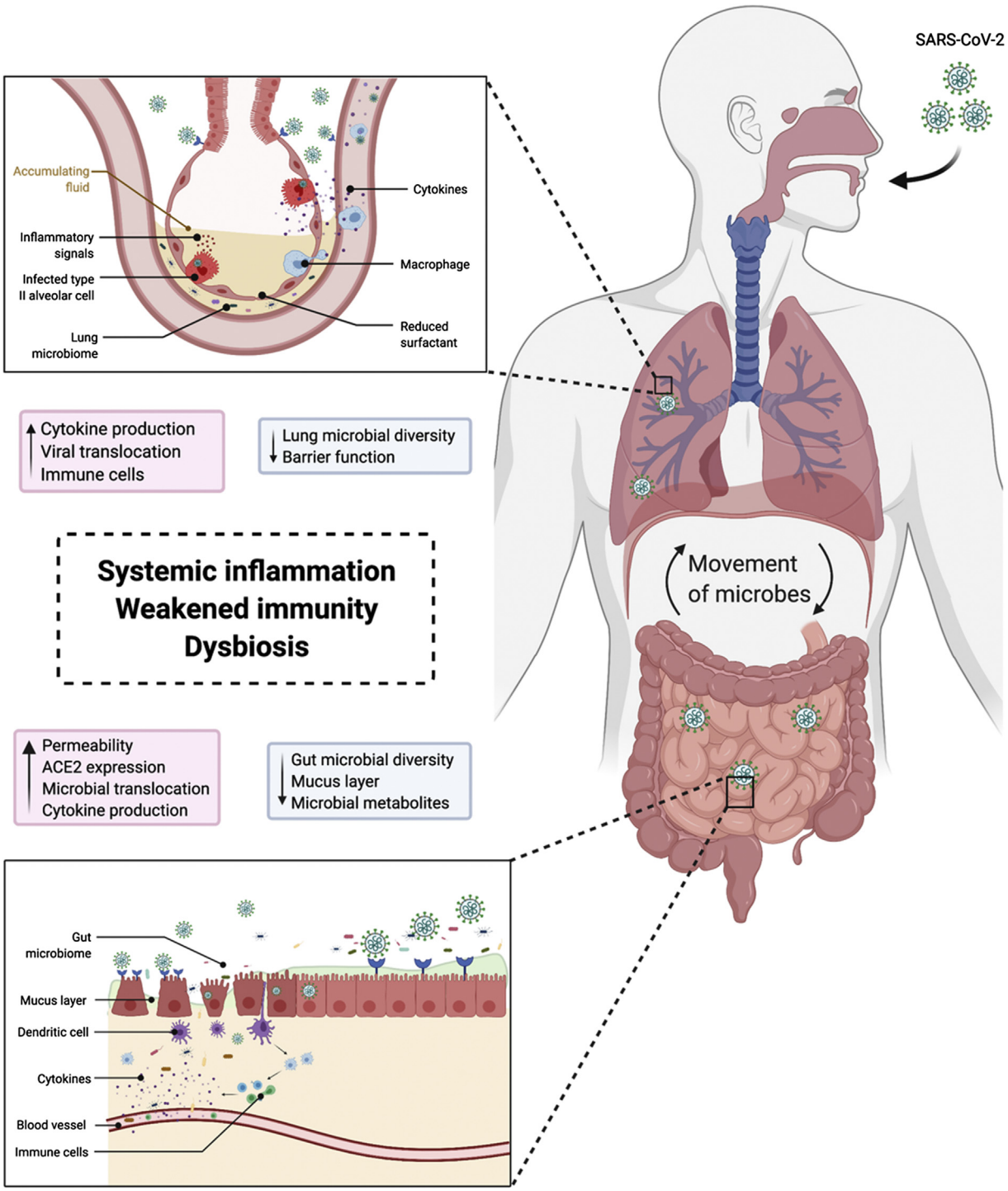

Fig. 2 SARS-CoV-2 Infection Impairs Gut and Lung Function. SARS-CoV-2 enters the respiratory tract and migrates to the lung (top panel). Epithelial, alveolar, and endothelial cells express angiotensin converting enzyme 2 (ACE2) and may be infected. In the infected cells pyroptosis is induced due to cell stress. Neighboring cells recognize the damage-associated molecular pattern (DAMPs). Subsequently, pro-inflammatory cytokines and chemokines (IL-6, IP-10, macrophage inflammatory protein 1α (MIP1α), MIP1β and MCP1) are released. Immune cells then migrate into the site of infection, promoting further inflammation. The loss of epithelial barrier function due to SARS-CoV-2 infection induces leakage and fluid accumulates in alveoli. The endothelium of the blood vessels may be infected by SARS-CoV-2, allowing for viral translocation into the blood and other organs. The hyper-inflammatory state reduces lung microbial diversity, while the overproduced cytokines travel throughout the body via the bloodstream and promote systemic inflammation. SARS-CoV-2 infection of the gut occurs within intestinal epithelial cells expressing the ACE2 receptor (bottom panel). Infected intestinal epithelial cells become dysregulated, thereby reducing their intestinal barrier function and inducing pro-inflammatory responses. Gut inflammation degrades the mucosal barrier, allowing for bacterial translocation and provides entry into the vasculature, thereby increasing a risk of secondary infections. Dendritic cells are attracted to the site of infection and activate macrophages, B- and T-cell

Disease prognosis of COVID-19 has been largely influenced by the multiorgan involvement (Zaim et al., 2020). Severe SARS-CoV-2 infection corresponds with increased pro-inflammatory cytokines the resultant cytokine storm (Huang et al., 2020). Moreover, SARS-CoV-2 infects the endothelium, the cells lining the blood vessels, which then allows viral particles to leak into the blood and circulate throughout the body (Varga et al., 2020). Ruan and colleagues reported significant differences in blood analysis between a COVID-19 deceased patients and COVID-19 recovered patients. Their study measured inflammatory markers in the blood, including white blood cell counts, platelets, lymphocyte counts, and IL-6 level. These researchers found 16% of the deceased patients suffered from secondary infections (Ruan et al., 2020). High levels of circulating pro-inflammatory cytokines may lead to altered gut microbiome composition, which subsequently leads to increased gut permeability. This may allow for the translocation of pathogens and toxins thereby increasing disease severity and multiorgan failure (Zaim et al., 2020). Interestingly, the combination of a dysbiotic gut environment and epithelial inflammation increase ACE2 expression in the gut. As ACE2 is the receptor for SARS-CoV-2, proinflammatory conditions within the gut microbiome create favorable conditions for infection (Chan et al., 2020). Kyo and colleagues found increased IL-6 levels to associate with ARDS severity (Kyo et al., 2019). IL-6 is one of the main cytokines produced in the gut during SARS-CoV-2 infection (Moore and June, 2020). Upon exposure to SARS-CoV-2, proinflammatory cytokines in response to lung infection also induce gut dysbiosis. Moreover, there is a positive feedback loop for cytokine production and inflammation, which worsens the prognosis for the COVID-19 patient (**Fig. 2**).

Conclusions and Perspectives

Probiotics are live microorganisms that when administered in adequate amounts present a health benefit on the host (Hill et al., 2014). Probiotics help to prevent bacterial and viral infections by ensuring a well-balanced and healthy microbiome (Hill et al., 2014). Specific probiotic strains may modify the dynamic balance between proinflammatory and immunoregulatory cytokines. This allows for viral clearance while limiting immune response-mediated damage to the lungs (Chong et al., 2019). Numerous clinical studies have focused on the use of probiotic supplementation to prevent or treat respiratory tract infections, and an in-depth review discusses this further (Lehtoranta et al., 2020). Additionally, studies have begun to investigate SCFAs supplementation during gut dysbiosis. In one study antibiotic treated or germ-free mice were given butyrate supplementation that stabilized hypoxia-inducible factor 1α (HIF-1α), a transcription factor that regulates expression of target genes in IECs which maintain barrier integrity (Kelly et al., 2015). Butyrate may also control SARS-CoV-2 replication and COVID-19 patients present with decreased SCFAs producing bacteria compared to healthy individuals (Li et al., 2021). Therefore, SCFAs supplementation and probiotic strains recognized to enhance barrier integrity may potentially help reduce SARS-CoV-2 infections.

The microbiome has a profound impact on human health. While the gut microbiome is a well-studied area, the molecular mechanisms mediating crosstalk between microbiome and host has not yet been fully elucidated. Research on lung microbiome complexity and how dysbiosis of the lung microbiome correlates with the development of respiratory diseases are expanding our understanding of the essential functions of the microbiome. Indeed, the gut-lung axis is an area of research that is providing new insights into how different microbiomes impact each other in healthy and disease states. Continued research into the crosstalk between these two distinct microbiomes at different anatomical locations may be key in understanding the immune response to infection and how to target it to prevent disease.

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mediated immune responses. Subsequently, pro-inflammatory cytokines, such as IL-6, are produced promoting further inflammation. ACE2 expression is upregulated due to inflammation, creating favorable conditions for further infection. A loss of microbial diversity, with a shift toward pathogenic microbes due to inflammation, reduces short-chain fatty acid production and results in a weakened systemic immune response and loss of barrier integrity. Gut dysbiosis alters the microbiome composition of the lung, whereas the systemic inflammation due to upregulated cytokine production in the lung alters gut microbiome composition. The crosstalk between the gut and lungs forms a positive feedback loop for increased inflammation and infection, worsening the damage to both organs. Source: Schematic drawn using biorender (www.biorender.com).

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