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The gut microbiome and severity of SARS-CoV-2 infection: what is the link?

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Abstract

In the recent years, studies of the human microbiome have aroused great interest. Several evidences suggest a connection between the gut microbiome and the human immune response at the pulmonary level, which has been defined as the "gut-lung axis". The clinical symptoms of COVID-19 are varied and include gastrointestinal manifestations such as diarrhea, which has been linked to alterations in the gut microbiome; imbalance of the immune response; and delayed viral clearance. The aim of this narrative review was to address the role of the gut microbiome in the respiratory health and in particular, its association with the severity of COVID-19. The gut microbiome plays several important roles therefore; its balance is determinant for the human health, due to its relationship with several essential physiological processes, including maturation of both of the innate and the adaptive immune responses. Intestinal dysbiosis has an impact on the respiratory mucosa, and in turn on infection of the intestinal epithelial cells by SARS-CoV-2, which can induce intestinal inflammation and gastrointestinal symptoms. All these symptoms could contribute to an altered inflammatory immune response to SARS-CoV-2, favoring infection, dissemination and severity of the disease. Knowledge about the roles of the gut microbiome and its interactions in the context of SARS-CoV-2 infection could help to find biomarkers involved in COVID-19-related dysbiosis, as well as to determine the possible therapeutic targets for treatment of these patients.

Keywords: Microbiota, COVID-19, Gut, Lung, Immunity response

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus; first appeared in China in December, 2019 and then rapidly spread worldwide (Wang *et al*., 2020). On January 30, 2020, the World Health Organization (WHO) announced the COVID-19 epidemic as an international public health threat, and subsequently on March 11, 2020, officially declared it as a pandemic (Cucinotta and Vanelli, 2020).

Clinical symptoms of COVID-19 can be manifested after 5-6 days of incubation, and they vary widely, ranging from an asymptomatic process to the appearance of several symptoms including; sore throat, dry cough, loss of taste and smell, nausea, shortness of breath, fatigue, myalgia, vomiting, diarrhea, pneumonia, multiple organ dysfunctions, and the development of acute respiratory distress syndrome (ARDS), finally leading to death (Huang *et al*., 2020). Advanced age and certain comorbidities such as obesity; hypertension and diabetes (all are associated with underlying inflammatory processes), are related to severity of the COVID-19 disease (Chinnadurai *et al*., 2020). In this regard, it is important to note that both aging and inflammation are interrelated complex systemic processes; involving participation of the immune mechanisms, in addition to other associated tissues such as the respiratory and gastrointestinal mucosal lining, which generate changes in the intestinal microbiome (Belkaid and Hand, 2014). The gastrointestinal tract has an extensive surface area, and in addition to its absorptive metabolic functions, it also harbors a robust immune system (Spahn and Kucharzik, 2004). The complex mixture of microorganisms that make up the intestinal microbiome contributes to the well-being of the human host. Such microorganisms influence the local and systemic processes that include among the other processes; vitamin delivery (LeBlanc *et al*., 2013), the nutrient transformation (Sonnenburg and Bäckhed, 2016); gut-lung communication (Dang and Marsland, 2019) and maturation of the mucosal immunity (Honda and Littman, 2016; Thaiss *et al*., 2016).

The objectives of this review were to discuss the roles of the gut microbiome in strengthening the human immune system, and the possible effects that alterations of the gut microbiome may have on the severity of SARS-CoV-2 infection.

2. The human gut microbiome

The term "microbiota" refers to the set of microorganisms that live both on the surface and inside the host, which include the bacteria; fungi, viruses, archaea and protozoa (Limon *et al*., 2017; Mirzaei and Maurice, 2017). In this sense, the human microbiota is made up of approximately as many microorganisms as the human cells (Sender *et al*., 2016).

On the other hand, the term "microbiome" refers to the total microbial community (microbiota); the genes encoded by it and the associated biomolecules (Lloyd-Price *et al*., 2016). In this context, the genes in the human cells are quantified as approximately 23,000 genes (Yang *et al*., 2009), while genes in the microbiome are around 3 million (Qin *et al*., 2010; Qin *et al*., 2012). The beneficial roles of our microbiome are the maturation of the immune system; the development of appropriate immune responses, and help in maintenance of the homeostasis. This information has long been known from several studies on the gut, which is the organ where the microbial population is most abundant (Lozupone *et al*., 2012; Brestoff and Artis, 2013).

The symbiotic balance between the host and the gut microbiome is very sensitive to several factors, such as; the genetic background of the host, the use of antibiotics or other medications, diet, and the presence of allergens or infectious agents. All these factors together with the capacity to alter the composition of

the microbiome and induce an imbalance are known as "dysbiosis" (Levy *et al*., 2017). Dysbiosis can lead to increased susceptibility to the new disorders, such as growth of the potentially pathogenic commensals (Weiss and Hennet, 2017).

Metagenomics studies, which include methods of amplification and sequencing of specific regions of the microbial DNA that in the case of bacteria target the 16S ribosomal gene (16S rDNA); a conserved region of the bacterial genome (Green *et al*., 2006), have allowed for more detailed and comprehensive definition of the gut microbiome of the healthy individuals. Moreover, these studies have provided knowledge about evolution of the gut microbiome throughout life, its dependence on diet, sex, geographical location, as well as on the body areas, and its alteration during the course of certain diseases (Ouwehand *et al*., 2004; Eckburg *et al*., 2005; Yatsunenko *et al*., 2012).

Several physiological functions are positively influenced by the gut microbiome. For example; development and maturation of the immune system is promoted by the emerging gut microbiome during the early childhood, and its activity is adjusted by the colonizing microorganisms throughout the human life (Belkaid and Hand, 2014). Consequently, dysbiosis has been associated with several acute and chronic inflammatory diseases (Lynch and Pedersen, 2016); however, the germ-free or microbiota-depleted animals are highly susceptible to several types of infections (Libertucci and Young, 2019).

In humans, the gut harbors the largest and most densely populated microbial ecosystem consisting of numerous species. However, bacteria are the most predominant microorganisms, and it is estimated that approximately 10^{11} - 10^{12} bacterial cells reside in the large intestine (Sjögren *et al*., 2009; Caballero and Pamer, 2015). The majority of the gut microbiome is composed of strict anaerobes; although facultative anaerobes and aerobes are also present (Sekirov *et al*., 2010). Despite of the large number of different bacterial phyla that have been identified; however, the overall bacterial population of the human gut is basically determined by only 2 genera namely; *Bacteroidete*s and *Firmicutes*, which account for approximately 92 % of the population. Meanwhile, other genera are also present including; *Proteobacteria*, *Verrucomicrobes*, *Actinobacteria*, *Fusobacteria* and Cyanobacteria (Eckburg *et al*., 2005; Cho and Blaser, 2012).

Evolution of the gut microbiome is intimately related to maturation; development and modulation of the intestinal immune response, regulating expression of the immune mediators, as well as the development and recruitment of the local immune cells (Sekirov *et al*., 2010; Caballero and Pamer, 2015).

Several previous studies on human newborns indicate that the early gut colonizers are acquired through contact with the maternals and with the environmental microorganisms (Palmer *et al*., 2007; Dominguez-Bello *et al*., 2010).This observation is supported by other studies evidencing an association between the composition of the infant gut microbiome and the route of birth in humans (Selma-Royo *et al*., 2020; Wilson *et al*., 2021). For example, vaginally born infants harbor microbial communities dominated by *Lactobacillus* spp. and *Bifidobacterium* spp., which are similar to those present in their mother's vaginal canal (Palmer *et al*., 2007; Biasucci *et al*., 2010). On the other hand, infants born by cesarean section are colonized primarily by common skin bacteria such as *Staphylococcus* spp. (Biasucci *et al*., 2010). These early colonizers carry the genes that determine the metabolism of sugars found in the breast milk, as well as those genes involved in the de novo synthesis of folate, which has critical metabolic functions in the gut (Yatsunenko *et al*., 2012).

During the first months of birth, an orderly developmental program takes place, where the composition of the gut microbiome as well as its functional capacity converge toward a mature configuration (Palmer *et al*., 2007; Biasucci *et al*., 2010; Koenig *et al*., 2011; Yatsunenko *et al*., 2012). This process is marked by significant dietary changes

involving the introduction of solid foods during weaning (Palmer *et al*., 2007; Fallani *et al*., 2011; Yatsunenko *et al*., 2012; La Rosa *et al*., 2014). During this transition state, the gut microbiome develops the ability to extract energy from the complex carbohydrates; metabolize the xenobiotics and participate in the biosynthesis of several vitamins such as cobalamin; biotin and thiamine; in addition, the gut microbiome adopts the characteristics of a mature microbiome (Nicholson *et al*., 2012).

3. Gut dysbiosis

When a set of microorganisms residing in a specific body area is maintained in equilibrium with the host (symbiosis), it is referred to as a healthy state. In contrast, disruption of this balance (dysbiosis) is associated with a disease, and is characterized by altered diversity and relative proportions of the microbial species (Cho and Blaser, 2012). The gut dysbiosis therefore refers to the imbalance in composition of the gut microbiome, compared to the pattern exhibited by an individual that is considered healthy (Weiss and Hennet, 2017). Gut dysbiosis can be caused by variety of factors, within which are: infection processes, aging, use of antibiotics, dietary changes, nutritional status, in addition to other medications including the anticancer drugs, gastric acid suppressing agents (Weiss and Hennet, 2017), and certain inflammatory conditions such as diabetes and obesity (Singer-Englar *et al*., 2019).

Numerous risk factors have been proposed in the pathogenesis of the intestinal dysbiosis, such as the use of antibiotics, especially when administered orally (Jernberg *et al*., 2007, Jakobsson *et al*., 2010). Alterations of the gut microbiome have also been demonstrated to take place under several conditions such as uptake of diets rich in fats, sugars and obesity (Turnbaugh *et al*., 2009; Ju *et al*., 2019). In this context, the use of certain drugs becomes particularly important. For example, metformin that is a standard drug used in the treatment of type 2 diabetes has been reported to affect the composition of the gut microbiome through elevating the *E. coli* levels (Forslund *et al*., 2015).

On the other hand, the conventional non-steroidal anti-inflammatory drugs, such as naproxen, ibuprofen and aspirin, alter the composition of the gut microbiome when administered for long periods of time, which results in an increase in members of the families *Bacteroidaceae* and *Enterobacteriaceae* (Rogers and Aronoff, 2016). Additionally, because the prolonged use of these drugs can lead to stomach ulcers; thus the proton pump inhibitors are usually prescribed in conjunction, to alleviate these side effects on the gastric and small intestinal mucosa. However, these drugs have also been observed to alter the gut microbiome, contributing to an increased risk of *Clostridium difficile*-associated diarrhea (Freedberg *et al*., 2015; Tsai *et al*., 2017), as demonstrated in Fig. (1).

4. The gut microbiome and its relationship with the immune system

Studying the gut microbiome and its connection to the functioning of the innate and adaptive immune systems is a growing and very active area of scientific research. Homeostasis of the immune system is achieved in part, through a complex interaction between the gut microbiome and the mucosal immune system (Peterson *et al*., 2015). The gut microbiome promotes the postnatal development of the immune system and calibrates its activity throughout life (Belkaid and Harrison, 2017). This occurs because the microorganisms present in the gut act as sources of antigens, which continuously stimulate the Gut-Associated Lymphoid Tissue (GALT), and accordingly the immune system (Wasilewska and Wroblewska, 2018). This interaction largely includes the involvement of cellular recognition receptors (i.e. Toll-like and NOD-type) and signaling metabolites such as the short-chain fatty acids (SCFA), which are produced by the colonizing microorganisms. Accordingly, these bacterial products can enter the circulation to reach the distant body sites (Clarke *et al*., 2010; Trompette *et al*., 2014).

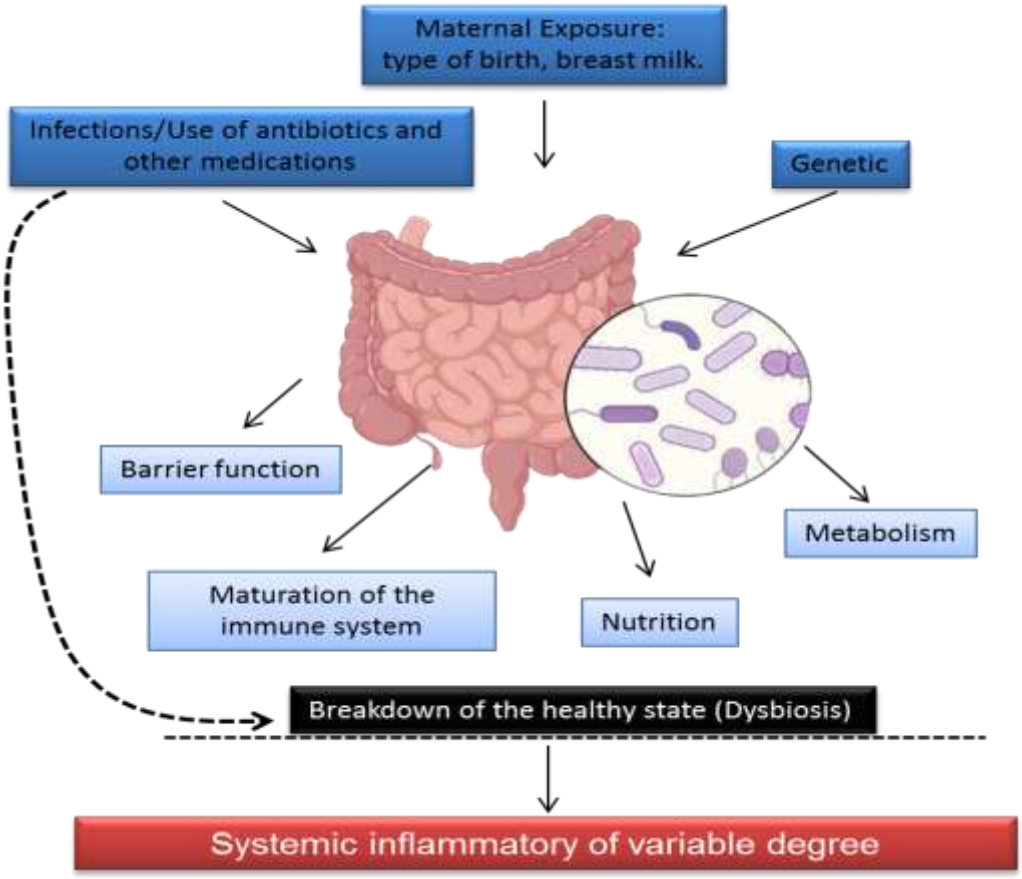

Fig. 1. Early microbial colonization results from several factors such as genetics, microbial exposure to both the mother and the environment, in addition to infection processes that require the use of antibiotics and\or other medications. This, in turn, sets in motion a cross-dialogue between the microbiome and the host, mediated by changes in nutrition; immunity, barrier function, metabolism and gene expression. The disruption of this balance leads to a dysbiosis, which can generate a systemic inflammatory process of varying degree associated with different disorders

The first evidences that the microbiome plays a key role in intestinal immunity arises from studies involving the germ-free mice (GFM) bred in a sterile environment, and the specific pathogen-free mice (SPFM) treated with broad-spectrum antibiotics, where the normal microbiota has been depleted (Macpherson and Harris, 2004). Such previous studies conducted on the various inflammatory contexts have revealed that the microbiome regulates both the innate and the adaptive immunity; with functional consequences for the host defense against the pathogens, in addition to immune tolerance to the non-pathogenic stimuli (Deshmukh *et al*., 2014; Khosravi *et al*., 2014). In this regard, SPFM have impaired myeloid cell development in the bone marrow, reduced numbers of circulating granulocytes, and are highly susceptible to the systemic bacterial infection (Deshmukh *et al*., 2014; Khosravi *et al*., 2014). Additionally, the innate lymphoid cells (ILCs), which are innate immune homologues of the CD^{4+} helper T cells; but unlike the latter lack the antigen-specific receptor expression, also exhibit developmental dysfunction in GFM. Similarly, interleukin-22 (IL-22) production by group 3 ILCs (ILC3) is significantly reduced in absence of

the microbiota, which is critical for the host immunity against the enteric bacterial infections (Britanova and Diefenbach, 2017).

Compared to SPFM, the GFM produce fewer intraepithelial lymphocytes (Bandeira *et al*., 1990), and show a significant decrease in the immunoglobulin A-secreting plasma cells in the lamina propria (Crabbé *et al*., 1968), in addition to fewer regulatory T cells (Treg) (Ostman *et al*., 2006). Meanwhile, the GFM also show a decrease in angiogenin-4 (Ang4) mRNA, a class of microbicidal protein that is secreted by Paneth cells in the intestinal lumen (Hooper *et al*., 2003). In addition, the Peyer's plaques in GFM contain a less developed germinal center than that recorded in the conventional mice (McDermott and Huffnagle, 2014).

The GFM and SPFM are valuable tools to assess the immunological effects of the various microbial species commonly found in the healthy gut microbiome. In this regard, GFM colonization with the segmented filamentous bacteria promotes germinal center formation and IgA production (Lecuyer *et al*., 2014), Th17 cell activation (Gaboriau-Routhiau *et al*., 2009) and IL-22 interleukin production by the ILC3 cells in the terminal ileum (Atarashi *et al*., 2015). These studies highlight the role of the intestinal microbiome in the regulation of the human immune system, and suggest that alterations in its composition may lead to the development of pathological processes involving both the intestinal and systemic immune activation.

The symbiotic relationship between the microbiome and the host is mutually beneficial. The host provides an important habitat and nutrients, whereas the gut microbiome supports development of the metabolic system and maturation of the intestinal immune system by providing beneficial nutrients, i.e. through vitamin synthesis (Kau *et al*., 2011) and short-chain fatty acids (SCFA) (McDermott and Huffnagle, 2014). However, the underlying mechanisms that would explain how the gut microbiome trains the immune system inside and outside the gut, as well as specific contribution of the bacterial species involved during interaction of the microbiome and the immune system components are still under study. Despite of this, Romani *et al*., (2015) reported that metabolites released by the gut microbiome, which are intermediate and/or end products of the dietary constituents of the commensal metabolism, can exert indispensable actions on the host immunity and health. For example, the non-digestible carbohydrates such as cellulose and the soluble dietary fibers are integral components of the human diet. However, humans lack the enzymes necessary to degrade these polysaccharides. In contrast, the anaerobic commensal bacteria that reside in the cecum and large intestine can ferment these fibers resulting in the generation of SCFAs such as propionate; acetate and butyrate. The host can detect these SCFAs through the butyrate receptor GPR109a8, the intracellular receptor PPARγ, and the surface proteins GPR41 and GPR43 (Alex *et al*., 2013).

In mammals, butyrate serves as the predominant energy substrate for the colonocytes and the enterocytes (Guarner and Malagelada, 2003; De Vadder *et al*., 2014). Propionate is taken up mainly by the liver, whereas acetate is released in the peripheral tissues (Guarner and Malagelada, 2003). In the human intestine, bacteria of the phylum Bacteroidetes secrete high concentrations of acetate and propionate, whereas bacteria of the phylum Firmicutes generate large amounts of butyrate (Guarner and Malagelada, 2003).

Administration of SCFAs leads to alterations in hematopoiesis, resulting in enhanced myeloid production due to the development of an elevated number of myeloid precursors (Balmer *et al*., 2014; Khosravi *et al*., 2014), which improves the allergic reactions (Trompette *et al*., 2014), and promotes clearance of the systemic infections (Balmer *et al*., 2014; Khosravi *et al*., 2014).

Another prominent example on how the microbiome causes the immune maturation at the tissue level involves the microbial metabolism of tryptophan. The commensal Lactobacilli; are shown to

utilize tryptophan as an energy source to produce the aryl hydrocarbon receptor (AhR) ligands, such as the metabolite indole-3-aldehyde (Zelante *et al*., 2013). AhR is a ligand-activated transcription factor of critical importance for the intestinal lymphoid follicle (ILF) organogenesis. AhR-expressing immune cells include RORγt+ innate lymphoid group 3 (ILC3) cells that are involved in ILF genesis; in addition, AhR expression is required for functional activation of the ILC3 cells (Kiss *et al*., 2011). Moreover, AhR-induced IL-22 production in the ILCs drives the secretion of the antimicrobial peptides including; lipocalin-2, S100A8 and S100A9, which contribute to protection from infection by *Candida albicans* (Zelante *et al*., 2013).

5. Relationship of the gut microbiome to the immune response at the pulmonary level

Several previous research studies have evidenced that changes in the composition of the gut microbiome generate multiple systemic effects (Gresse *et al*., 2017; Martinez *et al*., 2017; Mashaqi and Gozal, 2019; Sharma and Tripathi, 2019). In this regard, some studies have shown that the gut microbiota dysbiosis critically affects the antimicrobial immune responses at the pulmonary level (Chunxi *et al*., 2020). For example, compared to the conventionally bred animals, GFM and/or SPFM mice are more vulnerable to lung infections of both bacterial and viral origins (Clarke *et al*., 2010; Ichinohe *et al*., 2011; Brown *et al*., 2017). In this regard, studies on SPFM have shown that the microbiome promotes the interferon gamma (IFN-γ)-induced macrophage antiviral activity; inflammasome activation, CD^{8+} T cell responses and antibody production during influenza virus infection (Ichinohe *et al*., 2011; Abt *et al*., 2012). In this context, the flavonoid-derived bacterial metabolite known as desaminotyrosine has been identified as a modulator of IFN-γ-induced antiviral responses (Steed *et al*., 2017).

Another study conducted by Oh *et al*., (2014) revealed that antibody production in response to trivalent inactivated influenza vaccine (TIV) in GFM or SPFM is impaired, but has been restored by oral reconstitution of the microbiota with a flagellated strain of *E. coli*. The TLR5 receptor-mediated flagellin sensing has promoted the plasma cell differentiation directly, and stimulated the lymph node macrophages to produce plasma cell growth factors.

Although these previously described reports revealed that microbiota depletion impairs the antiviral immunity during infection and after vaccination; however, they have indicated also that the microbiome composition or diet influences susceptibility to the viral infection. Indeed, due to difference in microbiome compositions, the free-living wild mice have expressed increased resistance to the influenza infection compared to the laboratory mice (i.e. free of specific pathogens), as reported by Rosshart *et al*., (2017). On the other hand, other previous studies on patients undergoing allogeneic hematopoietic stem cell transplantation have showed an association between the butyrate-producing gut bacteria and protection against the lower respiratory tract viral infections (Haak *et al*., 2018).

In addition, experiments with GFM have shown that absence of the gut microbiota induces a state of decreased interleukin-10 (IL-10)-mediated inflammatory response, making these animals drastically susceptible to *Klebsiella pneumoniae* infection (Fagundes *et al*., 2012). Similarly, the alcohol-fed mice are more susceptible to *K. pneumoniae* infection, in part, due to the alcohol-induced intestinal dysbiosis (Samuelson *et al*., 2017). Previous studies of Clarke *et al*., (2010); Clarke, (2014); Brown *et al*., (2017) demonstrated that the microbiota is a source of peptidoglycan, which systemically stimulates the innate immune system, thereby enhancing neutrophil destruction of two important pathogens: *Streptococcus pneumoniae* and *Staphylococcus aureus* . This requires signaling through two pattern recognition receptors namely; NOD1 and NOD2.

Gauguet *et al*., (2015) study has reported that defense against *Staphylococcus aureus* pneumonia in

mice is dependent on pulmonary IL-22 production, which is promoted by intestinal colonization with the segmented filamentous bacteria (SFB).

The intestinal microbiome also influences infection with Mycobacterium tuberculosis. In this regard, mice treated with a cocktail of antibiotics have shown an increased susceptibility to infection by this bacterium, which correlates with a decrease in the number of IFN-γ and TNF-α producing Th1 cells, in addition to an increase in the populations of the Treg cells (Khan *et al*., 2016).

Moreover, it is worth mentioning that, an increased population of the butyrate-producing bacteria in the intestinal microbiome is associated with increased resistance to the viral respiratory infection (Haak *et al*., 2018). Meanwhile, a recent study that used an experimental model of influenza virus infection in mice has shown that infection with the virus concomitantly caused an alteration in the composition of the intestinal microbiota, and impairment of the barrier properties of the intestine, accompanied by a decrease in SCFA production, thus favoring secondary enteric bacterial infection (Sencio *et al*., 2021).

The above mentioned evidences have indicated that the gut microbiome contributes to maintenance of the body homeostasis and regulates the immune responses both at the gastrointestinal level and in the distant organs, such as the lungs. The possible mechanisms involved, include; development of immune tolerance through the regulatory T cells Tregs, regulation of the T cell populations outside the gastrointestinal tract, regulation of the systemic inflammatory response and production of SCFA (Samuelson *et al*., 2015; Chunxi *et al*., 2020).

6. Intestinal dysbiosis and its association with the severity of SARS-CoV-2 infection

Numerous research studies have revealed the importance of the intestinal microbiome on the maturation; development and quality of the immune response both locally and systemically (Al Nabhani and Eberl, 2020; Weström *et al*., 2020; Oh *et al*., 2021). This is in addition to the relationship between the intestinal microbiome and the immune response at the pulmonary level, which has made it possible to describe what is known as the intestine-lung axis (Enaud *et al*., 2020). This axis suggests that modifications of the intestinal microbiome affect the immune responses of the respiratory tract (Dang and Marsland, 2019). For this reason, it is perfectly rational to establish a connection between the gut microbiome and the evolution of SARS-CoV-2 infection.

The gastrointestinal symptoms are frequent in patients with COVID-19 (Han *et al*., 2020). In this regard, the angiotensin II-converting enzyme (ACE2) used by the SARS-CoV-2 to enter the human cell is widely expressed on the surface of the enterocytes (Zhang *et al*., 2020). Presence of SARS-CoV-2 RNA, the nucleocapsid protein and ACE2 has also been observed in the epithelial cells of the stomach, esophagus, rectum and duodenum (Xiao *et al*., 2020). Moreover, RNA fragments are recorded in the stool samples collected from the infected patients (Chen *et al*., 2020; Park *et al*., 2021). Additionally, alteration of the intestinal microbiome has been described in patients with COVID-19, which opens the possibility that SARS-CoV-2 infection may induce dysbiosis (Zuo *et al*., 2020; Gu *et al*., 2020). Similarly, a study conducted by Yeoh *et al*., (2021) has showed that the composition of the gut microbiota in patients with COVID-19 correlates with the disease severity, which is characterized by a decrease in certain species such as *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and several species of *Bifidobacterium*. Such dysbiosis has persisted after viral elimination.

As previously mentioned the SARS-CoV-2 utilizes the ACE2 molecule; a member of the renin angiotensin system (RAS), to enter the host cell through the S1 subunit of the receptor binding domain (RBD). This process is facilitated by the trans-membrane serine protease-2 (TMPRSS-2) and ADAM metallo-peptidase domain 17 (ADAM17) (Patel *et al*., 2014; Hoffmann *et al*., 2020, Gupta *et al*., 2021).

The ACE2 molecule plays a key role in the regulation of hemodynamics at both the tissue and systemic levels. ACE2 acts as a counter-regulator of the angiotensin-converting enzyme (ACE) activity; primarily by converting the angiotensin I peptide (Ang I) to angiotensin 1-9 (Ang 1-9), and the angiotensin II (Ang II) to the vasoprotective molecule angiotensin 1-7 (Ang 1-7) (Vitiello and Ferrara, 2021). Angiotensin II is a peptide with pro-inflammatory, profibrotic and vasoconstrictive properties, and has the capacity to increase the oxidative stress and blood pressure; these effects are mediated mainly after its binding to type 1 receptors (AT1R). On the other hand, Ang (1-7) binds to the Mas receptor (MasR) and promotes antioxidant, vasodilation and anti-proliferative effects, which are antagonistic to the action of Ang II (Azushima *et al*., 2020). Therefore, the RAS consists of two fundamental axes, mainly; the axis shaped by ACE2/Ang (1-7)/ MasR, which counteracts the second axis shaped by ACE/Ang II/AT1R, as presented in Fig. (2).

Fig. 2. Simplified view of the renin angiotensin system. The RAS is present locally and systemically. Angiotensin II is the main effector of this system, which through its receptor (AT1) is able to induce pulmonary damage. During SARS-CoV-2 invasion, ACE2 decreases its expression in type II alveolar epithelial cells, which generates a decrease in the conversion of Ang II to Ang (1-7). This impedes the protective action of Ang (1-7) by acting on its receptor (Mas R). This favors the activation of the ACE/AngII/AT1R axis and consequently decreases the activity of the ACE2/Ang-(1-7)/ MasR axis. (Ang I: angiotensin I, Ang II: angiotensin II, Ang-(1-7): angiotensin 1-7, Ang(1-9): angiotensin 1-9, MasR: G protein-coupled receptor Mas, AT1R: angiotensin II receptor 1)

The ACE2/Ang (1-7)/ MasR axis promotes vasodilatation, blood pressure lowering and has anti-inflammatory activity; whereas the second axis promotes vasoconstriction; has pro-apoptotic, pro-fibrotic and pro-inflammatory activities, in addition, it stimulates the oxidative stress (Azushima *et al*., 2020).

Taking this context into an account, it is important to note that SARS-CoV-2 competes with Ang II for binding to the ACE2 molecule. This induces a blockade of the ACE2 activity and therefore reduces expression of the enzyme (Cheema and Pluznick, 2019). This down-regulation of ACE2 promotes ACE/ ACE2 imbalance and increases pathological activation of the ACE/Ang II/AT1R axis, leading thus to an increase in Ang II-mediated vasoconstriction, and a decrease in (Ang 1-7)-mediated vasodilation (Kotfis and Skonieczna-Żydecka, 2020).

The association between the intestinal dysbiosis and ACE2 enzyme activity in the gastrointestinal tract is poorly understood. However, studies carried out in knock-out mice for the ACE2 molecule have shown an increased susceptibility to dysbiosis, colitis and intestinal inflammation, which are induced by the epithelial damage (Viana *et al*., 2020). On the other hand, older adults with reduced ACE2 levels and RAS alteration as observed in the cases of hypertension, kidney disease and diabetes, are at increased risk of dysbiosis, and these pathologies increase the risk of mortality by COVID-19 (Cole-Jeffrey *et al*., 2015; Simões *et al*., 2016; Malek Mahdavi, 2020; Zhang *et al*., 2021). In addition to inflammation and ACE2 dysfunction, hypoxia that is a frequent clinical symptom recorded in patients with COVID-19; could be implicated in the occurrence of gastrointestinal symptoms, as it is known to be critical in the case of intestinal homeostasis, which includes the composition and functions of the microbiome (Singhal and Shah, 2020).

Most of SARS-CoV-2 infections may be asymptomatic or cause mild symptoms in approximately 80 % of the recorded cases (Wang *et al*., 2020). However, in approximately 10-20 % of the cases, the patients may progress to an interstitial pneumonia and ARDS; especially in those individuals who have older age and associated comorbidities (Jordan *et al*., 2020; Sharma *et al*., 2021).

Data related to disease progression suggest that an underlying chronic inflammatory state may influence the severity of COVID-19, rather than the direct cytopathic effects of SARS-CoV-2 (Brodin, 2021). Interestingly, most of the risk factors associated with COVID-19 severity are related to a persistent and low-grade inflammatory process; as described in several pathologies such as aging; obesity, diabetes and hypertension (Vas *et al*., 2020; Brodin, 2021). However, all these conditions have been related to dysbiosis.

A previous study of Sato *et al*., (2014) highlighted that dysbiosis is characterized by an increased translocation of the bacteria across the intestinal epithelium. In the healthy intestine, small amounts of translocated commensal bacteria are eliminated by the action of Th1 and Th17 lymphocytes, which are particularly induced by polysaccharides of *Bacteroides* spp. (Mazmanian and Kasper, 2006), and by the segmented filamentous bacteria attached to the mucosa (Ivanov *et al*., 2009). However, high numbers of the invading bacteria and permanent activation of the Toll-like receptors lead to overproduction of the pro-inflammatory cytokines, which damage the intestinal epithelium and cause chronic intestinal inflammation (Karczewski *et al*., 2014).

The role of gut dysbiosis in the immune responsiveness is especially evident in the older adults. Imbalance of the gut microbiome associated with aging has been sufficiently described, and a decrease in *Bifidobacteria*, *Lactobacillus* and the bacteria producing SCFA such as butyrate; that are necessary to maintain the integrity of the intestinal barrier, has been reported by Mangiola *et al*., (2018); Nagpal *et al*., (2018).

Early in the SARS-CoV-2 outbreak, older adults have been observed to account for a disproportionate number of severe cases and deaths (Wang *et al*., 2020), which have been corroborated by several epidemiological and observational studies (Nikolich-Zugich *et al*., 2020; Onder *et al*., 2020; Ruan *et al*., 2020). Advanced age is considered as one of the main risk factors for COVID-19 complications. "Immunosenescence" is a term used to describe the age-related changes, where alterations in the immune system have been described as key determinants of the outcomes of infection with SARS-CoV-2 (Nikolich-Zugich *et al*., 2020; Pedreañez *et al*., 2021).

Among hallmarks of the immune system, aging is associated with persistence of a pro-inflammatory state. Because of this association between advanced age and inflammation; the term "inflammatory aging" has been coined in 2000, to describe a constant and low-grade inflammatory state, which is characterized by the production of inflammatory mediators above the basal concentration (Franceschi *et al*., 2000). The elevated levels of pro-inflammatory factors in the older adults can have both local and systemic consequences. This increase in circulating levels of the pro-inflammatory cytokines and the other factors are considered to be determinant in the development and maintenance of immunosenescence (Franceschi *et al*., 2000; Solana et al., 2012), and contribute in the development of chronic diseases of the lung and the other organs (Hearps *et al*., 2012; Franceschi and Campisi, 2014).

Several studies suggest that COVID-19-associated mortality is primarily attributed to the excessive inflammatory response; with the consequent release of large amounts of cytokines and chemokines, which contribute to the virus-induced hyper-inflammation that is termed as the "cytokine storm" (Huang *et al*., 2020; Ruan *et al*., 2020). Therefore, taking into account the high mortality rates due to COVID-19 among the older adults and people with underlying comorbidities, in addition to the presence of gut dysbiosis frequently observed under these conditions, it is feasible to hypothesize that perturbations of the gut microbiome could influence the disease severity and clinical course of COVID-19 (Villapol, 2020; Kalantar-Zadeh *et al*., 2020), as shown in Fig. (3).

In a recent study conducted by Yeoh *et al*., (2021) where 100 patients diagnosed with SARS-CoV-2 infection have been evaluated, results have shown that the composition of the gut microbiome is significantly altered in patients with COVID-19, compared to the healthy individuals. A decrease has been observed in several gut commensals with immunomodulatory potentials, such as *Eubacterium rectale*; *Faecalibacterium prausnitzii* and *Bifidobacteria*, which remained low in the samples collected up to 30 days after disease resolution. Furthermore, one of the most interesting aspects of this study is that dysbiosis observed in these COVID-19 patients has correlated with the disease severity; assessed through increased concentrations of the pro-inflammatory cytokines and the other blood markers including the C-reactive protein, in addition to the enzymes gamma-glutamyl transferase; lactate dehydrogenase and aspartate aminotransferase (Yeoh *et al*., 2021).

Another study conducted by Gu *et al*., (2020) evaluated the composition of the gut microbiota in 30 patients with COVID-19; 24 patients with influenza A (H1N1) and 30 healthy controls. Results have shown that patients with COVID-19 have a significantly reduced bacterial diversity; an abundance of several opportunistic pathogens, such as *Streptococcus*, *Actinomyces*; *Rothia* and *Veillonella*, in addition to lower abundance of the beneficial symbionts.

Similarly, Zuo *et al*., (2020) performed a metagenomic sequencing analysis on the fecal samples collected from 15 patients with COVID-19 in Hong Kong. Results demonstrated that those patients have significant alterations in the fecal microbiota compared to the controls. Moreover, these fecal samples have been characterized by enrichment of the opportunistic pathogens and depletion of the beneficial commensals; where the gut dysbiosis persisted even after clearance of the SARS-CoV-2 and resolution of the respiratory symptoms.

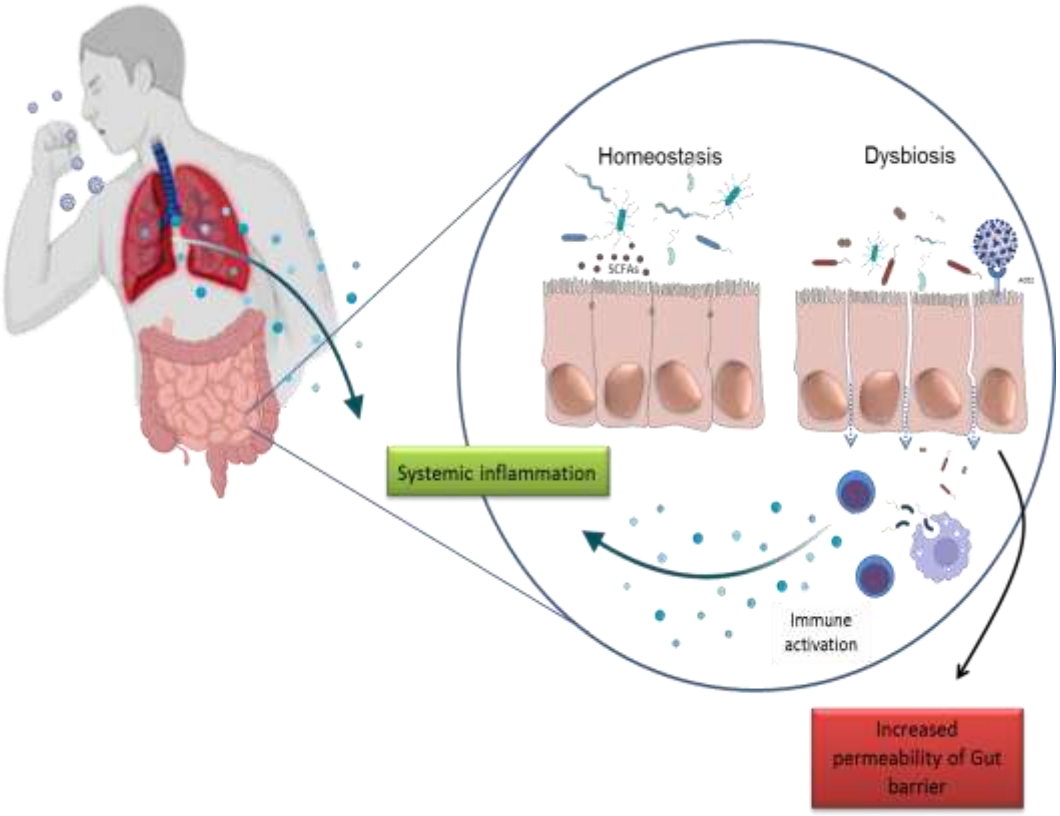

Fig. 3. Schematic representation of the role of the gut-lung axis in COVID-19. The gut-lung axis is bidirectional, meaning that metabolites derived from the intestinal bacteria affect the lung via the blood, while inflammation of the lung modifies the intestinal microbiota. During SARS-CoV-2 infection, the virus can infect the lung cells and can also translocate through the circulation to the digestive tract, where SARS-CoV-2 binds to ACE2 on enterocytes. Dysbiosis of the intestinal microbiota as a consequence of infection breaks the integrity of the intestinal barrier. Inflammation in the gut induces altered permeability leading to translocation of bacterial antigens and toxins into the circulation, resulting in systemic inflammation

Another interesting study conducted at Rush University Medical Center (RUMC) where plasma samples from 60 SARS-CoV-2 positive individuals with varying degrees of severity and 20 negative controls have been analyzed, and reported that severe COVID-19 is associated with high levels of zonulin, which is a marker of tight junction permeability and translocation of the bacterial and fungal products into the blood such as LPS and β-glucan. This marker of altered intestinal barrier integrity and microbial translocation correlates strongly with the higher levels of markers of systemic inflammation and immune activation, lower levels of markers of intestinal function, altered plasma metabolome and glucome, and higher mortality rate (Girón *et al*., 2021).

It has been recently reported by Yonker *et al*., (2021) that children with multi-systemic inflammatory syndrome have prolonged presence of SARS-CoV-2 in the gastrointestinal tract, which results in the release of zonulin; with subsequent trafficking of the SARS-CoV-2 antigens into the bloodstream, thus triggering a state of hyper-inflammation. Increased zonulin levels indicate disruption of the tight junctions in the

intestinal epithelium, which may allow leakage of SARS-CoV-2 derived antigens into the bloodstream (Yonker *et al*., 2021). Zonulin release can be induced by various stimuli such as dysbiosis (Serek and Oleksy-Wawrzyniak, 2021).

Conclusion

The gut microbiome performs several important functions, such as metabolizing the nutrients, resisting pathogenic colonization, maintaining the intestinal barrier and educating the immune system. Therefore, its balance is detrimental for the human health, due to its relationship with several essential physiological processes including maturation of both the innate and the adaptive immune responses. As have been discussed in this review, the intestinal dysbiosis has an impact on the respiratory mucosa, and infection of the intestinal epithelial cells by SARS-CoV-2 can induce dysbiosis; intestinal inflammation and gastrointestinal symptoms. In addition, the intestinal dysbiosis is a phenomenon observed in several comorbidities such as type 2 diabetes; obesity, hypertension, coronary artery disease, and in other aging-related disorders. Dysbiosis is associated with altered inflammatory immune response due to SARS-CoV-2, thus favoring infection; dissemination, and severity of the disease in these patients. It is unclear to what extent the composition of the gut microbiome is influenced by clinical management of these COVID-19 patients. However, caution is needed when interpreting the results, i.e. taking into account the antibiotic use, as many patients with COVID-19 receive antibiotic therapy empirically. Further studies are therefore needed to improve our knowledge about the role of the gut microbiome and its interactions in the context of SARS-CoV-2 infection.

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Conflict of interest

The authors declare no conflict of interests.

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Ethical approval

Non-applicable.

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