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SARS-CoV2 an Enteric Virus?

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ABSTRACT

The human body is an ecosystem that harbors trillions of microbes that interacts in a coordinated way to sustain a healthy life. Gut microbiota (GM), one component of this ecosystem, includes a set of commensal and pathogenic microorganisms. Qualitative and quantitative diversity of GM depends on different environmental factors. These complex communities have a crucial role in the fight against infections and the maintenance of immune homeostasis.

Patients infected by a SARS-CoV2 virus, a new coronavirus disease 2019 (COVID-19), present respiratory and gastrointestinal symptoms with varying degrees of severity. The lungs are the primary target organs for infection via the ACE2 receptor. However, clinical studies show that the gut can also be targeted because the ACE2 is more expressed in the gut cells. Thus, all this suggests that SARS-CoV2 leads to dysbiosis of the lung and gut microbiota, indicating a direct and indirect link with GM and infection.

This review will highlight the interactions between immune host and microbes during viral infection and predict the implication of GM in COVID-19 disease modulation. This crosstalk would identify biomarkers to characterize the pathology and target the GM may be an alternative route to restore homeostasis and prevent infection by SARS-CoV2.

KEYWORDS

Gut microbiota; Immune response; SARS-CoV2; Alternative therapy

ABBREVIATIONS

AMPs: Antimicrobial Peptides; GM: Gut Microbiota; SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus 2; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; COVID-19: Coronavirus Disease 2019; ACE2: Angiotensin Converting Enzyme 2; IgA: Immunoglobulin A; RNA: Ribonucleic Acid; miRNAs: microRNA; IEC: Intestinal Epithelial Cells; SCFA: Short-Chain Fatty Acids; LPS: LipoPolySaccharide; HIV-1: Human immunodeficiency virus

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INTRODUCTION

To date, there are seven beta coronavirus known to infect humans, the last of which appeared in 2019, SARS-CoV2, causing respiratory and intestinal pathologies. SARS-CoV and MERS-CoV have a great similarity with SARS-CoV2 regarding the structure and severity of the pathology [1-3].

ACE2, human epithelial receptor for SARS-CoV2, which is found in the lungs and intestine, ensures the cellular entry of the virus and its replication [4].

Common symptoms of COVID-19 disease are fever, cough, tiredness, myalgia, and dyspnea. Although the incidence of gastrointestinal symptoms is low, the virus is found in the stool in almost half of the patients. These data suggest a possible involvement of GM during SARS-CoV2 infection [5-6].

The gut microbiota is composed of autochthonous and allochthonous microorganisms belonging to different domains: Archaea, Bacteria, and Eukarya, as well as viruses [7]. The qualitative and quantitative composition of the gut microbiota is affected by several internal and external host environmental factors [8], including host genetic, diet, age, mode of birth, ethnicity and antibiotic consumption [9-11]. Moreover, the host produce several molecular signals such as antimicrobial peptides (AMPs), and immunoglobulin A (IgA), miRNAs by the intestinal epithelial cells (IEC), to control the structure of the surfaces colonized by microbiota and so influences its composition [12]. Also, it has been suggested that probiotic can alter the composition of the gut microbiome, which in turn changes the host metabolism [13]. Obesity, insulin resistance, fatty liver disease, and low-grade peripheral inflammation are more prevalent in patients with low α diversity in the gut microbiome [14,15]. The latter is also important in the development and modulation of the immune system [16-18], affecting much more host functions such as metabolic functions, nervous system functions [19-22].

In this review, we try to highlight the possible crosstalk between gut microbiota and SARS-CoV2 during infection while detailing the interactions between the different components of the intestinal microbiota, particularly the virome and the bacteriome, and their impact on the host's immune system.

GUT MICROBIOTA COMPONENTS AND THEIR INTERACTIONS

Composition and Role of Microbiota

The human body is colonized by a microbiota housed mainly in the mucous membranes of all human organs. The intestinal microbiota is the one that contains the greatest diversity and abundance in microorganisms [23]. This microbiota is influenced by internal and external environmental factors (age, sex, diet, genetics, etc.) [24-26]. However, the genetic modifications of the microbiota are much faster and more important than that of the human host, thus underlining the very marked impact of the microbiome in human evolution [27]. The studies carried out on the intestinal microbiota have mainly focused on the qualitative and quantitative evaluation of the bacterial component then of the viral component. On the other hand, the other microorganisms such as fungi, helminths, arches has long been neglected [28].

Thanks to technological advances, the characterization of the human gut microbiota and the associated microbiome constituted a challenge to determine the composition of microorganisms and understand their role. The bacteriome is mainly composed of four phyla: *Firmicutes, bacteriodetes, actinobacteria and proteobacteria* [29], which play main role in host metabolism, including digestion and absorption of nutrients, the synthesis of certain vitamins and enzymes as well as the production of short-chain fatty acids (SCFA) [30]. In addition, these bacteria have demonstrated a positive effect on the integrity of the intestinal barrier, proliferation and

differentiation of epithelial cells, protection against pathogens and modulation of the immune system [30].

The virome, the second component of microbiota, corresponds to viruses detected in gut human. It includes the eukaryotic viruses responsible for infections of host cells, the prokaryotic viruses responsible for the infection of bacterial communities of the microbiota, and the Archean-viruses which infect the archaea. As well as the endogenous viral sequences conserved in the human genome during evolution [31]. The composition of the virome consists essentially of bacteriophages, which are thought to play a crucial role in the selection and establishment of intestinal bacterial communities. The gut virome is highly personalized and its composition remains stable for over a one year (Table 1) [32]. Both eukaryotic and prokaryotic viruses have lytic and latent life cycles, favoring interactions between the virome, bacteriome and the host leading to the survival and evolution of the viruses [33].

Virome Type	Virome Family	References
Prokaryoticviruses *(bacteriophages)*	*Siphoviridae*	[138]
	Inoviridae,	
	Myoviridae	
	Podoviridae	
	Myoviridae	[139]
	Podoviridae	
	Siphoviridae	
	Microviridae	
	Microviridae	[140]
Eukaryotic viruses	*Retroviridae*	[141]
	Pneumoviridae	[142]
	Anelloviridae	
	Herpesviridae	[143]
	Hepadnaviridae	[144]
	Hepeviridae	
	Polydnaviridae	
	Tymoviridae	
	Virgaviridae	
	Picornaviridae	[141]
	Reoviridae	
	Picornaviridae (Enterovirusgenus)	[145]
	Papillomaviridae (AlphapapillomavirusGenus)	[146]
	Papillomaviridae (BetapapillomavirusGenus)	
	Papillomaviridae(GammapapillomavirusGenus)	[146]
	Polyomaviridae	
	Adenoviridae	[138]
	Adenoviridae (GenusMastoadenovirus)	
	Circoviridae (CircovirusGenus)	[147]
	Anelloviridae	
Eukaryotic viruses	*Anelloviridae(GyrovirusGenus)*	[147]
	Parvoviridae (BocaparvovirusGenus)	[148]
	Parvoviridae (ProtoparvovirusGenus)	[148]
	Astroviridae (MamastrovirusGenus)	[149]
	Reoviridae (Rotavirus Genus)	[149]
	Caliciviridae (Norovirus Genus)	
	Picornaviridae (EnterovirusGenus)	[147]
	Picornaviridae (ParechovirusGenus)	[148]
	(Picornaviridae (CosavirusGenus)	
	Picornaviridae(KobuvirusGenus)	
	Picobirnaviridae (PicobirnavirusGenus)	[149]
	Reoviridae (rotavirus Genus)	[149]
	Astroviridae (astrovirusgenus)	

Table 1: Human virome family in the gastrointestinal tract.

Human eukaryotic viruses affect the physiology of the host upon infection while altering the expression of genes and gene products of the host [34-36]. Like the bacteriome, the virome can have a positive effect on

intestinal homeostasis and modulation of the immune system. Indeed, Kernbauer et al., 2014, have demonstrated that a common enteric RNA virus can replace the beneficial function of commensal bacteria in the intestine [37]. Therefore, coordinated interactions between human virome and commensal bacteria could be a way to understand the host's response to viral infection and its evolution.

Bacteriome and Virome Interplay

Bacteriophages interactions with bacteria play a very important role both in the modulation of host-bacteria interactions and in the regulation of the virome [38]. These bacteriophages influence the structure and function of these bacterial communities. Phages can serve as important reservoirs of genetic diversity of the microbiota by acting as vehicles for horizontal transfer of virulence, resistance to antibiotics, and metabolic determinants in bacteria [39]. The phages behave differently depending on their intestinal location and the infected bacteria; they can adopt a lytic life cycle by diverting the cell replication machinery leading to the release of newly formed phages. In contrast, temperate phages incorporate their genetic material into the host's cell chromosome in the form of prophage and replicate alongside this host cell. In some cases, temperate phages do not integrate into the bacterial genome and exist as circular or linear plasmids in the host bacterial cell, this will prevent hijacking of the cell replication machinery and cell death [40,41]. Thus, this suggests that bacteriophages can affect human health by contributing to or modifying the metabolic capacities of the resident bacterial community. For example, the filamentous phage CTX infects Vibrio cholerae, by injecting its genetic code which carries the CTX gene coding for toxins. The V. cholerae having integrated the viral genetic code containing the CTX gene multiply rapidly by releasing toxins. These toxins alter the epithelial cells of the intestinal mucosa. Then, the bacteria produce and release more phages, allowing their dissemination [42,43]. Bacteriophages directly and indirectly modulate intestinal physiology and the immune response, by shaping the composition and function of the bacterial microbiome [44,45]. Bacteriophages can infect commensal or pathogenic bacteria, inducing their lysis and promoting a change in the bacterial composition of the intestinal microbiota [46]. As feedback, the bacteriome can boost the intestinal epithelium of the host and consequently enhance the immune responses [47,48].

Eukaryotic viruses, both commensal and pathogens are less numerous than bacteriophages in the intestine, otherwise they have an important effects on human health and modulate intestinal physiology [49,50]. Interactions between viruses and bacteria, and other constituents of the intestinal microbiota, are therefore important in influencing the course and outcome of viral infections [50,51]. The question is to understand how enteric viruses' resident in the gut can affect the physiology of the host beyond the disease. Eukaryotic gut viruses may have an impact on the host's defense mechanisms against pathogenic viral or bacterial infections. Indeed, certain viral infections provide a benefit to the infected host for other infections. This has been demonstrated with latent murine herpes virus infections in mice which by enhancing immunity protect the mouse from many other infections [28,52]. The viral disease will, therefore, depend on the interaction of microbes and viruses with the host's genes [53].

The gut microbiota can either promote or inhibit viral infection in host cells. Several studies have highlighted the dual interaction that can exist between viruses and bacteria of the microbiota in the intestine. Monedero et al. 2018 and Karst and al., 2015 have discussed the complexation of enteric viruses and antigens of the blood groups synthesized by commensal bacteria [54,55]. This association between these two components can be both beneficial for the virus, ensuring its penetration into the host cell and subsequently its development, and for the host by eliminating and destroying the virus [54,55]. In the

same context, other studies have shown the effect of antibiotics on the infectious power of rotavirus [56,57]. Viral infectivity is also reduced in mice treated with antibiotics. The absence of antibiotic treatment allows Bacillus cereus to produce secondary metabolites that trigger a toxic shock syndrome similar to that induced by LPS [58]. Thus, Kuss et al. (2011) have reported that poliovirus binds lipopolysaccharide and peptidoglycan of bacteria and subsequently enhances viral infectivity [59]. Other in vitro studies carried out on human B cells infected with norovirus in the absence of intestinal microbiota confirms the results obtained in vivo, namely a reduction in the infectious power of the virus [60-62]. Bacteria can play a dual role in the face of a viral infection, allowing viral replication in the host cell and the progression of chronic infections, or inhibiting viral infections [63]. Notably, the Lactobacillus has been shown to effectively block viral infections caused by rotavirus [55]. Furthermore, the induction of intestinal inflammation by sodium dextran sulfate in laboratory animals has shown a reduction in this inflammation in the presence of the intestinal virome. Therefore, the enteric virome can also play a protective role in the immune response [64,65]. Likewise, the bacterial microbiota influences immunity to a variety of eukaryotic viruses. In fact, pre-existing antibodies to enteric bacteria have been shown to interfere with responses to HIV-1 vaccines [66].

Most studies of the microbiome suggest common elements between bacteriome, virome, and host genetics [53]. In addition to the interactions between the virome and the bacteriome, the interaction between the host and all microbiota elements has been strongly suggested. However, this interconnectivity is so complex that understanding their direct relationships is difficult, giving rise to few studies in this direction. Indeed, these interactions could modulate the pathogenic power of the virus [31].

The immune responses of the host are determined according to the diversity and the distribution of virome and bacteriome [67]. The interaction of bacteria and virus stimulates innate host immunity by macrophages, that induce an adaptive immune response via T lymphocytes releasing pro-inflammatory cytokines [37,68]. Excessive pro-inflammatory responses by promoting T cells and their subsets T helper 1 (Th1) releasing pro-inflammatory cytokines such IFN-γ and TNF-α, induce self-regulation of the host immune system through Treg cells which reduce inflammation [50]. Thus, the immune-modulatory effect of the microbiome promotes immune tolerance to the microbiome and immune homeostasis. Therefore, an imbalance in the gut microbiota can play an important role in the development of autoimmune and chronic diseases. The disruption of the gut microbiota leads to cross interactions between microbe-microbe and microbe-host, which determine the host's response [69].

GUT MICROBIOTA AND SARS-COV2

SARS-CoV2 Enteric Eukaryotic Virus

SARS-CoV2 found in the stools of symptomatic and asymptomatic patients indicates that this virus could be considered as an enteric virus forming part of the intestinal virome [5,6].

A study carried out on three family clusters reported the persistence of viral RNA in the stools of pediatric patients with SARS-CoV2 for longer than 30 days. While in the respiratory tract, viral RNA is undetected 2 weeks after abatement of the fever [70].

The incidence of gastrointestinal symptoms, namely anorexia, abdominal pain, nausea and vomiting and diarrhea is higher in severely affected patients compared to patients with a low severity rate, respectively 66.7% *vs.* 30.4%, 8.3% *vs.* 0%, 6.9% *vs.* 4.6%, 5.8% *vs.* 3.5% [71]. These symptoms, indicative of metabolic disorders, are known to affect the gut microbiota and therefore cause dysbiosis. Indeed, a recent study analyzing a biopsy on esophageal, gastric, duodenal and rectal tissues, in a patient (with viral ARN in stool) showed that the protein

ACE2 is strongly expressed in all tissues except esophageal cells, supporting the entry of SARS-CoV2 into the host cells [6]. ACE2 is a cell receptor, known to be abundant in the epithelia of the lungs and intestine in humans. The existence of structural similarity between the SARS-CoV and SARS-CoV2 receptor binding domains means that the latter can use ACE2 as a cell entry receptor despite the presence of amino acid mutations in the SARS-CoV2 receptor binding domains [72]. Thus, the study of Zhou P et al. notably confirmed that SARS-CoV2 uses the same ACE2 receptor as SARS-CoV [73]. Thus, this suggests that the gastrointestinal tract may be a target organ for SARS-CoV2 [74] and that ACE2 could play a dual role in mediating sensitivity and immunity of SARS-CoV2 infection [75-79]. Lamers, 2020, have reported that enterocytes in human small intestinal organoids were readily infected by SARS-CoV2, supporting viral replication. The mRNA expression analysis in infected enterocytes revealed upset of viral response program [80,81].

Also, it has been shown in a study conducted by Zuo et al. (2020) on patients with COVID-19 without gastrointestinal disorder, presence of SARS-Cov2 RNA in stool, suggesting 'quiescent' gastrointestinal infection of SARS-CoV2. Patients with a high SARS-CoV2 viral load in stool, exhibit an abundance of *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis* and *Morganella morganii* and increase of nucleotide, amino acid biosynthesis and carbohydrate metabolism. Whereas, patients stool with a low-to none SARS-CoV-2 infectivity signature had a higher abundance of short chain fatty acid producing Bacteria, Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii and Lachnospiraceae bacterium1_1_57FAA [81].

All this data strongly suggests that infection with SARS-CoV2 could shape the microbiota, and promote other infections with pathogenic bacteria. On the other hand, SARS-CoV2, once in the intestine, could infect the host's intestinal epithelial cells via the ACE2 receptor, hijacking its function and altering its expression [82]. Infection of intestinal epithelial cells causes greater dysbiosis when linked to age-related comorbidities. Conversely, the gut microbiota directly modulates the expression of the ACE2 enzyme, leading to inflammation [83]. The question asked here, is to determine the interplay that could exist between the three major elements: SARS-CoV2 virus, gut microbiota and immune response, based on the known interactions.

Gut-Lung-Immune System Axis and SARS-CoV2

The intestinal microbiota has been widely studied, particularly in the maturation and development of the immune system, as well as in the cross-interaction between these two components. The gut is the first site of interaction between host immune system and microorganisms. During a respiratory infection, it has been shown a relationship between the gut and the lung microbiota [68,84].

The microbial population of the lung is less densely populated than those of other body organs. Maintaining a less dense bacterial community in the lungs seems to be a sign of good health. Colonization of the lungs by microorganisms is ensured by the inhalation-microaspiration process digestive tract. The resulting composition depends on the process of microbial elimination and environmental conditions [85,86]. The most abundant genera in the lungs of healthy individuals are Prevotella, Streptococcus, Fusobacteria, Pseudomonas, and Veillonella. Other potential pathogens: Haemophilus and Neisseria are less represented [87-91]. Veillonella spp., Fusobacteria and Prevotella spp., anaerobic bacteria originating from the oropharyngeal microbial flora, are the minor constituents of the local microbiota; they are also present during pulmonary inflammation. This microbiota plays a crucial role in both acute and chronic pathologies, particularly in the progression and severity of the pathology. Bacteria of this

pulmonary microbiota are implicated in the chronicity of the inflammation generally leading to pulmonary aggravations disease [85]. A secondary bacterial infection is a common complication of viral infection, especially for respiratory viruses that often significantly increases morbidity rates [92,93]. In the case of cystic fibrosis, bacteria from the intestinal microbiota are found in the pulmonary microbiota, which means the presence of cross-communication between these two microbiotas, suggesting a host wide network [94,95]. Addedly, during acute respiratory infection, the weakened membranes become more permeable, thus facilitating the passage of bacteria between the intestinal compartment and the pulmonary compartment. This induces intestinal and pulmonary dysbiosis impacting inflammation response and evolution of the infection [96].

Lung microbiota is associated with the susceptibility and severity of COVID-19 disease [85]. Alterations in this component could potentially modify immunological homeostasis, by altering the immune response against secondary viral and bacterial infection [97]. Indeed, the interconnection between host cells and microorganisms during a viral infection induces the secretion of pro-inflammatory cytokines, amplifying the impact of the viral infection [92,93]. Thus, like the gut microbiome, the pulmonary microbiome has a role in regulating the immune response [24]. A disturbance in bacterial diversity of gut microbiota in patients with a very severe COVID-19 infection has been detected. In addition, a significant decrease in Bifidobacterium, Lactobacillus, and Eubacterium, as well as a significant increase in pathogenic bacteria such as *Corynebacterium* and *Ruthenibacterium* have been observed [98,99]. Several bacterial intestinal microbiota biomarkers are identified, for instance, during viral infections, biomarkers of the genus Lactobacillus positively correlates with inflammation (IL-6 and IFN-γ) [100,101], while the genus Blautia is positively associated with IL-10 [102-104]. Gou et al. (2020), in their study, predict a positive correlation between a 10% increase in the blood Proteomic Risk Score (PRS) and a 57% risk that the infection will become even more severe, this suggests that the composition of the intestinal microbiota could be at the origin of the predisposition of normal individuals to a severe COVID-19, and the adoption of PRS as a protein biomarker to determine the risk or severity of COVID-19 infection [68,105,106]. This severity is mainly due to an excessive pro-inflammatory response, namely cytokine storm [107,108]. Regulation of this cytokine storm is necessary to prevent a worsening of COVID-19 patient's status which can lead to death. Indeed, the secondary metabolites of the intestinal microbiota mentioned above interact directly with CD4 +T and CD8+T cells, releasing pro-inflammatory cytokines such IFN-γ and TNF-α, induce self-regulation of the host immune system through Treg cells which reduce inflammation [109]. Effectively, the microbiota is involved in the activation and differentiation of a memory phenotype of CD8+T lymphocytes, through its secondary metabolites such as short-chain fatty acids (SCFA) and butyrate (Figure 1) [108]. In fact, it has been shown that mice treated with rich fiber diet and which are injected with LT specific for HSV, show better proliferation of effector CD8+T lymphocytes and an increased production of soluble mediators such as IFN-γ, that is a cytokine involved in the antiviral response [108]. Influenza virus infection has been shown to induce anorexia, which reduces the production of SCFAs by the microbiota, and therefore the proliferation and differentiation of CD8+T effector [109]. Intestinal dysbiosis will take place, promoting bacterial superinfection, which worsens the patient's state of health. In addition, desaminotyrosine (DAT), a metabolite produced by *Clostridium orbiscindens*, protects against influenza through increased of type I INF signaling and decreased pulmonary immunopathology [110]. All of this data could have major implications for understanding the mechanisms and interactions that can take place between the microbiota and SARS-CoV2. In fact, in convalescent

COVID-19 patients, measuring CD4+ and CD8+T cells reached higher levels, respectively 100% and 70%, compared with individuals unexposed to SARS-CoV2 [111]. This suggests an alteration in the gut microbiota of COVID-19 patients, affecting the metabolism of gut bacteria and consequently the level of SCFAs.

The symbiotic relationship between the gut microbiota and the immune system is the result of a homeostatic co-evolution leading to an interactional dynamics in the gut-lung-immune system axis in SARS-CoV2 infection.

TOWARDS PROMISING COMPLEMENTARY THERAPY?

Diet, Viral Infection and Immune System

Nutrition and lifestyle are important factors to maintain the balance of the transkingdom and overcome viral infection. In infected people, the body needs energy and nutrients to fight the virus, which requires a healthy and balanced diet rich in vitamins, essential fatty acids, minerals, prebiotic and probiotic [112-115]. Indeed, individuals with metabolic syndrome seem to have more severe symptoms of COVID-19, suggesting an altered immune response [106,116]. A French study has shown an evolution in the severity of COVID-19 infection in obese people. The prevalence of obesity in patients with critical COVID-19 is higher than in patients with non-critical COVID-19 [117]. Immuno-senescence and age-related changes in the gut microbiota lead to increased mortality of COVID-19 patients [118]. Thus, nutritional support and the application of prebiotics or probiotics have been suggested to regulate the balance of the intestinal microbiota and reduce the risk of secondary infection due to bacterial translocation [74,119,120]. In mice, a diet enriched in fibers and SCFA protects against respiratory inflammation, by regulating the immune system. The intestinal microbiota can thus influence the pulmonary microbiota and regulate the immune response of the lungs [121,122]. The secondary metabolites of the intestinal microbiota (LPS, SCFA), as well as the immune T cells of the intestine, are transported by the blood to the lungs. The intestine-lung and immune system axis suggest the cross-modulation of the three components (Figure 1) [85].

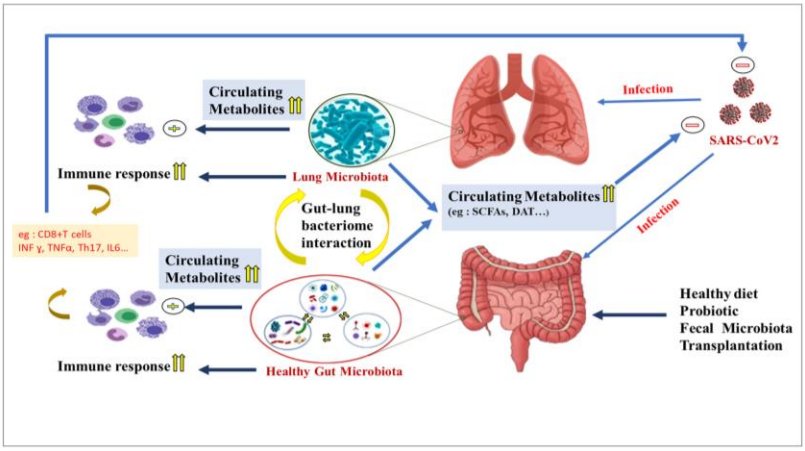

Figure 1: Potential interactions between lung-gut microbiota during SARS-CoV2 infection.

In this context, China's National Health Commission and National Administration of Traditional Chinese Medicine suggested the use of probiotics in patients with severe COVID-19. Indeed, the role of probiotics in reducing the secondary effects of antibiotic treatment and the susceptibility to subsequent viral infections has been demonstrated [123-125]. The use of lactobacillus as probiotics are effective in reducing antibiotic-associated diarrhea [126]. Two separate meta-analyses have reported moderate effectiveness of probiotics in reducing the incidence and duration of viral respiratory tract infections [127,128]. Other studies have shown a decrease in the

severity of pneumonia when patients are treated by a cocktail of probiotics [129-131].

Finally, the use of probiotics can constitute a complementary treatment to restore homeostasis and reduce the duration of antibiotic treatment of patients with COVID-19.

Fecal Microbiota Transplantation: Another Therapeutic Route?

Fecal microbiota transplantation (FMT) is a therapeutic approach, which has been used for a long time to rebalance the intestinal microbiota. In humans, the first transplants of fecal microbiota were performed in the context of recurrent Clostridium difficile infections [132]. This therapeutic approach has since been tested in many pathologies such as chronic inflammatory bowel diseases, metabolic diseases, or even neuropsychiatric diseases where dysbiosis has been observed [133]. Also, this intestinal dysbiosis has been detected in HIV-positive patients infected with HIV, accompanied by a decrease in intestinal CD4 levels, signifying a decrease of the immune system response [134]. Taking these data into account, a study carried out on macaques infected by the Simian Immunodeficiency Virus treated with FMT showed stimulation of the immune system with the intestinal microbiota rebalancing [135]. Additionally, in the case of co-infection with porcine circovirus type 2 and porcine reproductive and respiratory syndrome virus, Niederwerder et al., (2018) have shown that the group of pigs transplanted with the fecal microbiota presents a significant reduction in morbidity and mortality compared to the control group, as well as an increase in the level of antibodies in the blood. This result suggests that FMT stimulates the host's immune system against viral agents, preventing viral replication. Thus, FMT could be a prevention tool against porcine circovirus associated disease [136]. Regarding the COVID-19 infection, many hypotheses based on the relationship between intestinal and pulmonary dysbiosis are being studied to search alternative therapeutic approaches as FMT. However, clinical trials started a few months ago, in particular concerning the treatment of COVID-19 patients by FMT, have been suspended due to the risk associated with viral transmission by FMT.

On the other hand, other clinical studies are underway to determine the diversity of the microbiota and the effect of probiotics in patients with COVID-19 [137].

CONCLUSION

The human body is a dynamic ecosystem in continuous evolution, whose genetic variations of hologenomes are the result of modifications of the host genomes and the genomes of symbiotic microorganisms under the effect of the environment. Nutrition and lifestyle are important factors to maintain the balance of the transkingdom and overcome viral infection. A disturbance in bacterial diversity of gut microbiota in patients with very severe COVID-19 infection has been detected. Thus, it is likely that intestinal dysbiosis can induce pulmonary dysbiosis affecting inflammation and infection severity.

Adopting a healthy lifestyle, use of probiotics or FMT can constitute a complementary treatment to restore homeostasis and reduce the duration of antibiotic treatment of patients with COVID-19. The perspectives of the results of ongoing clinical trials could provide strong arguments in favor of the use of probiotics as a promising therapy.

CONFLICT OF INTEREST

Badreddine Nouadi, Yousra Sbaoui, Abdelkarim Ezaouine, Rida Mohamed Salam, Mariam El Messal, Faïza Bennis and Fatima Chegdani declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors contributed conception and design of the study. BN, YS, RS and AZ wrote section II and part of section III of the manuscript. FC, MM and FB, wrote

sections I, part of section III, Abstract and Conclusion of the manuscript.

All authors contributed to manuscript revision, read and approved the submitted version.

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