The Gut Microbiome versus COVID-19

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The Gut Microbiome versus COVID-19

Olga Vasieva[1,2] and Igor Goryanin[3,4]*

[1]*Ingenet Ltd, 27 Market Street, Hoylake, UK*
[2]*Institute of Integrative Biology, University of Liverpool, Liverpool, UK*
[3]*School of Informatics, University of Edinburgh, UK*
[4]*Okinawa Institute of Science and Technology, Okinawa, Japan*

Abstract

The digestive system is an environmental frontline involving digestive secretions, intestinal cell metabolism, and gut microbiome that significantly modulate multiple functions in organisms. Understanding the 'gut-lung axis', where gut residential microbiota play important roles, may help in the development of better prophylactics and intervention strategies for diseases caused by respiratory viruses, including coronavirus disease of 2019 (COVID-19). Gastrointestinal symptoms are common in COVID-19 patients and are generally indicative of disease complications. As we have learned so far, diarrhea and gut dysbiosis during SARS-CoV-2 infection should not be ignored, as they can be used to distinguish pathways of dysregulation of the immune system and the regulatory pathways upstream and downstream of viral primary binding receptors such as ACE2. This review presents evidence of microbiome signatures in the gut and respiratory system that may predict the severity and long-term outcomes of COVID-19. Understanding the factors (such as pro-inflammatory trends, modulation of metabolite availability, and impact on cell signaling and pathogenic properties) translating the effect of microbiome composition on the severity of respiratory infections should help in the development of new approaches for health monitoring, disease prevention, and treatment.

Keywords: GM • Microbiome • COVID-19 • SARS-CoV-2 • Dys-biosis • ACE2 • Immune system • Gut-lung axis

Abbreviations: SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2 • SARS: Severe Acute Respiratory Syndrome • COVID-19: Coronavirus Disease of 2019 • MERS: Middle East Respiratory Syndrome • RSV: Respiratory Syncytial Virus • GM: Gut Microbiome • GI: Gastrointestinal • IBD: Irritable Bowel Disease • ACE2: Angiotensin Converting Enzyme 2 • IFN-I: Type I Interferon (IFN-α) • B(O)AT1: Sodium-dependent Neutral Amino Acid Transporter • mTOR: The Mammalian Target of Rapamycin.

Introduction

The digestive system is an environmental frontline involving digestive secretions, intestinal cell metabolism, and gut microbiome (GM) [1,2] that significantly modulate multiple organism's functions organisms [3]. Nutrients and prebiotics provide substrates for a dynamic GM, which is estimated to consist of over 1000 different microbial species belonging to five predominant phyla: Firmicutes, Bacteroidetes, Actinobacteria, Verrucomicrobia, and Proteobacteria [4-7]. Approximately 400 identified species are strictly anaerobic and hence will generally be found in mucosal regions such as the oral cavity and the gastrointestinal (GI) tract [2,6].

Two thirds of the GM is considered an individual-specific 'fingerprint' [2,8]; however, there are correlations found between GM composition and diet [1,9-11], geography, ethnicity [11-15], age, and longevity of the host [10,14-17], and certain diseases [8,18-22]. GM characteristics of members of the same family cluster in functional and taxonomic space, stressing the role of environmental and genetic factors in the evolution of an individual's GM [23].

Gut virome composition also appears to be unique to and varies with people's age and geography, with few viral populations shared within a subset of people. There are 33,242 unique viral populations (97.7% of which are phages) that have been identified in the human gut [24]. As is the case with the microbiome, consistent variations in viral diversity could also be seen in healthy versus sick participants [25].

***Address for Correspondence:** Igor Goryanin, School of Informatics, University of Edinburgh, UK, Tel: +447720897334, E-mail: goryanin@oist.jp*

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The current global COVID-19 pandemic [26] is caused by a beta coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), that in the most vulnerable individuals can cause an immune response resembling cytokine storm syndrome [27], a dysregulated secretion of cytokines that triggers systemic inflammation and hypercoagulation, and, in children, a multisystem inflammatory syndrome that resembles Kawasaki disease [28]. Approximately 20% of patients with COVID-19 develop serious complications, often accompanied by fatal acute respiratory distress syndrome.

Increasing evidence points to an intimate relationship between the gastrointestinal and respiratory tracts, which is known as the 'gut-lung axis' [29-31]. The intestinal flora is involved in host nutrient absorption and metabolism and has a profound impact on all organ systems, human health, and disease [7,32–35].

However, intestinal microflora disorders reduce host antiviral immune responses, thereby aggravating the lung damage caused by these infections [36]. Changes in the lung microbiota were identified in COVID-19 patients, with a shift towards bacteria found in the intestinal tract correlating with the onset of acute respiratory distress syndrome. Probiotics have already been recommended for anti-viral therapy and prophylactics [37,38].

Literature Review

In this review, we bring together data pointing to the potential significance of modulation of the gut microbial community and its functional influence on the organism's immunity and resistance to prophylactics and treatment of COVID-19 disease. These factors should be addressed as we prepare for future challenges.

COVID-19 gastrointestinal manifestations

GI symptoms in COVID-19 patients are generally indicative of complications. However, they are common in these patients, with a meta-analysis showing that the symptoms were present in 17.6% of infected patients

[39,40]. Similarly, approximately 25% of patients with SARS and MERS exhibited GI symptoms [41,42].

Studies have detected SARS-CoV-2 RNA in anal swabs and stool samples from almost 50% of patients with COVID-19 [43-46]. mRNA analysis demonstrated that the duration of viral shedding from stool was longer than that from respiratory samples [47], suggesting that the digestive tract might be a site for virus replication and activity. Prolonged digestive symptoms, especially diarrhea, are negatively correlated with gut microbiota richness and composition [48,49], and are accompanied by elevated levels of fecal calprotectin, an indicator of inflammatory responses in the gut [50]. It should, however, be noted that gut microbiome dysbiosis is also characteristic of diabetes, obesity, autoimmune, and aging-related diseases, all of which are associated with an increased risk of severe COVID-19 [13].

GM dysbiosis is associated with COVID-19 disease

Comorbidities commonly accompanying severe COVID-19 are known to be associated with alterations in bacterial taxa from the phyla Bacteroidetes and Firmicutes [51-54], which were reported to regulate angiotensin-converting enzyme 2 (ACE2) expression in rodents [55]. Assessment of GMs of COVID-19 hospital patients conducted in China [56] showed that the abundance of *Coprobacillus, Clostridium ramosum*, and *Clostridium hathewayi* species positively correlate, while the abundance of *Faecalibacterium prausnitzii* (an anti-inflammatory bacterium) negatively correlates with COVID-19 severity. During hospitalization, abundancies of *Bacteroides dorei*, *Bacteroides thetaiotaomicron*, *Bacteroides massiliensis*, and *Bacteroides ovatus* were inversely correlated with SARS-CoV-2 load in fecal samples from the patients. However, gut dysbiosis persisted even after clearance of SARS-CoV-2 from the throat and resolution of respiratory symptoms.

Changes in GM composition may be indicative of shifts in nutritional availability in the gut, which could be due to the diet, pharmacological interventions, or absorptive properties of the gut endothelium. Fecal samples with high SARS-CoV-2 mRNA load had an abundance of bacterial species with higher capacity for glycolysis, de novo nucleotide synthesis, and amino acid biosynthesis (e.g., *Collinsella aerofaciens*, *Collinsella tanakaei*, *Streptococcus infantis*, *Morganella morganii*), whereas fecal samples with low-to-none SARS-CoV-2 mRNA had a higher ratio of short-chain fatty acid-producing bacteria [57,58] of the *Parabacteroides*, *Bacteroides*, *Alistipes*, and *Lachnospiraceae* genera [59]. Another important finding was the significant depletion of butyrate-producing bacteria in H1N1 patients versus healthy controls [60,61], suggesting that butyrate may be involved in the modulation of inflammation during viral pneumonia. This is supported by the observation that a high-fiber diet, which increases the production of short-chain fatty acids, enhances the antiviral CD8+ T-cell immune response during influenza virus infection, attenuates neutrophil-mediated lung injury, and consequently improves survival [36,62]. MRx-4DP0004, a strain of the butyrate-producing bacterium *Bifidobacterium breve*, originally developed for asthma treatment [63], has shown the potential to downregulate specific pathological aspects of the hyper-inflammatory response while maintaining the appropriate antiviral response. However, significantly reduced levels of butyrate producers were linked to overgrowth of pathogenic bacteria and increased intestinal mucosal permeability and endotoxin intoxication and, consequently, inflammation with cytokine release [64-66]. Recent studies further suggest that gut microbiome composition may predict a predisposition to severe COVID-19 due to a hyper-inflammatory response [49].

Gut microbiome and viral infections shift in GM composition

An increase in the proinflammatory component in GM has also been observed for other respiratory viruses such as influenza [67]. In a lemur model, several commensal taxa, essential for a healthy gut microbiome, decreased, whereas the abundance of potential pathogens, such as Neisseria, increased upon adenovirus infection [68].

The clinical manifestations and transmission routes of seasonal influenza A (H1N1) are similar to those of COVID-19 [69], and a comparison of the microbiota in these two diseases was of interest from etiological and diagnostic perspectives. The microbial signature associated with detectable levels of SARS-CoV-2 mRNA was similar to that of other respiratory viruses such as influenza and respiratory syncytial virus (RSV) (ignoring the small sample size of the study) [70]. However, patients with H1N1 displayed lower diversity and different overall microbial composition compared with COVID-19 patients, and biomarkers were proposed for distinguishing the two cohorts [71].

COVID-19 patients still had significantly reduced GM bacterial diversity, significantly higher relative abundance of opportunistic pathogens such as *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces*, and lower relative abundance of beneficial symbionts, compared with healthy controls. Changes in the enteric environment and immune factors caused by *Actinomyces*, particularly, were shown to aggravate the damage caused by inflammatory bowel disease [60,72], and an association of Actinomyces with COVID-19 infection may also have a prognostic value.

Compared with healthy individuals, levels of *Agathobacter*, *Fusicatenibacter*, *Roseburia*, and *Ruminococcaceae* UCG-013 in COVID-19 patients were depleted and negatively correlated with levels of inflammatory markers (CRP, procalcitonin, or D-dimer). Moreover, CRP and D-dimer levels were positively correlated with COVID-19–enriched bacteria (*Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces*). In the H1N1 cohort, there was a positive correlation between inflammatory cytokines; IL-2, IL-4, and IL-6, and abundance of *Finegoldia*, *Anaerococcus*, *Peptoniphilus*, *Intestinibacter*, and *Prevotella* genera [71].

Understanding whether the composition of the GM can be modified to improve the outcome of viral respiratory infections, particularly in COVID-19 patients, is of great significance.

Immune system modulation by gut microbiome in COVID-19 and other viral diseases

One of the ways in which microbiota can be involved in disease progression is by affecting the inflammatory state of the gut and the systemic levels of proinflammatory cytokines.

Higher abundance of *Klebsiella*, *Streptococcus*, and *Ruminococcus* genera correlated with elevated levels of proinflammatory cytokines and increased disease severity, while increased levels of Lactobacillus species correlated with higher levels of anti-inflammatory IL-10 and improved disease prognosis [49]. Cases of COVID-19-induced Kawasaki disease-like complications in young children [28,73] were also associated with dysbiotic gut microbiome, with increased levels of *Streptococcus* and decreased levels of *Lactobacillus* species compared with healthy children [74]. Compared with healthy individuals, COVID-19 patients had significantly higher systemic levels of IL-6 and TNF-α, and levels of cytokines IL18 and IgA in the gut were also affected by COVID-19 infection [75]. High IL18 and IgA levels correlated with overrepresentation of the previously mentioned *Streptococcus* genera, as well as *Clostridium* and *Bifidobacterium*. Increased abundance of *Lactobacillus* was correlated with high IL18 expression and poor prognosis, as well as a lack of the genera *Bacteroidetes*, *Roseburia*, *Faecalibacterium*, *Coprococcus*, and *Parabacteroides* in COVID-19 patients relative to healthy controls [75].

The proinflammatory gut environment is characteristic of patients suffering from a range of conditions, including diabetes, obesity, irritable bowel disease (IBD), and high blood pressure, which are typically correlated with the severity of COVID-19. One can expect some degree of causation between GM composition and the disease-promoting environment; however, the vector in the link still needs to be validated in larger patient cohorts or in an experimental setting (although this option is more problematic).

Both innate and adaptive immune system responses are triggered by SARS-CoV-2 infection. However, in severe COVID-19 patients, the numbers of B cells, CD4+ and CD8+ T cells, and monocytes are lower [76,77]. GM is a known modulator of the immune system [78,79], and the immune system plays a leading role in gut colonization by microbiota, as the development of regulatory T cells and innate lymphoid cells help maintain gut and lung homeostasis. Microbial metabolites regulate the host immune system [80-83] and may also participate in the immune response triggered by viral replication in the gut.

Butyrate and other short-chain fatty acids and desaminotyrosine produced by *Bacteroidetes* and/or *Clostridium* [81,84], for instance, can enhance influenza-specific CD8+ T-cell function [78] and Type I interferon (IFN-I) signaling in macrophages, increasing protection against influenza infection [85-88]. Microbiota-derived acetate also protected against respiratory syncytial virus infection through an interferon response in mice [65]. The typical gut microbiota also enhances antiviral immunity by increasing the number of immune cells and decreasing immunopathology.

Respiratory viruses are known to influence microbial composition in the lung and intestines. Respiratory influenza infection, for instance, causes intestinal injury when lung injury occurs by recruiting lung-derived CCR9+CD4+ T-cells to the small intestine and stimulating the production of interferon-γ by these cells [88,89]. Microbiota-driven signals triggered the IFN-I response in the lung stroma as a defense against early viral infection.

Influenza-infected individuals may also develop GI symptoms as observed in COVID-19 patients [89], although replication of the influenza virus occurs almost entirely in the respiratory system. It was demonstrated that IFN-I molecules produced in the lungs supported a depletion of obligate anaerobic bacteria and enrichment of Enterobacteriaceae in the gut [61], which could have been the cause of the observed proinflammatory dysbiotic gut environment [61], promoting further virus infectivity.

Role of ACE2 in the gut microbiome shifts during COVID-19

A cell surface receptor, angiotensin-converting enzyme 2 (ACE2), is associated with cardiopulmonary disease, and alterations in the gut and/or lung microbiome have recently been suggested to play a role in this pathology [90,91]. Single-cell transcriptome analysis showed that ACE2 was highly expressed in lung alveolar epithelial type II (AT2) cells, stratified epithelial cells in the upper esophagus, and enterocytes in the ileum and colon [92]. ACE2 expression is downregulated in patients during SARS infection [93], and ACE2 was confirmed as the target of SARS-CoV-2 [94-96].

A dysbiotic gut environment and epithelial inflammation cause an increase in the levels of ACE2, affecting dietary amino acid homeostasis, innate immunity, and gut microbial ecology [49,97]. Expression of ACE2 is regulated by gut bacteria; representative species of Bacteroides genus, for instance, are known to downregulate the expression of ACE2 in the murine gut [98]. Proinflammatory gut microbiome, on the contrary, can elevate ACE2 expression and promote conditions favorable for SARS-CoV-2 infection of the gut epithelium [99], from where it can spread through the body [100,101]. In turn, by binding to ACE2, SARS-CoV-2 may interfere with nutrient absorption and disrupt intestinal homeostasis (Figure 1). ACE2 regulates the activity of the sodium-dependent neutral amino acid transporter B(0)AT1, which controls the intestinal uptake of tryptophan [97,102]. Tryptophan regulates the expression of antimicrobial peptides, an important component of the homeostatic regulation of GM composition, through the mammalian target of rapamycin (mTOR) pathway (Figure 1) [103,104]. ACE2 downregulation, therefore, should decrease the secretion of antimicrobial peptides, leading to increased pathogen survival and gut dysbiosis. ACE2-dependent regulation of the microbiota may explain the occurrence of diarrhea in SARS-CoV and SARS-CoV-2 infections [54,96]. ACE2 might also be associated with cardiopulmonary pathology via alterations in the gut and/or lung microbiome [90].

It is worth noting that, although ACE2 facilitates viral entry at the epithelial surface, it offers protection against acute lung injury. The ACE2 functional circuit [91] can be carefully adjusted to confront SARS-induced tissue injury, and it is becoming clearer that GM plays some part in this homeostatic mitigation [105]. Clinical trials have shown that administration of ACE2 can reduce systemic inflammation [106].

Gut-Lung axis and Lung microbiomes

COVID-19 associated with GM-led processes crosstalk is summarized in Figure 2. Lung microbiome composition also undergoes a shift during viral infection, and, unexpectedly, typical GM resident bacteria become abundant in the lung microbiome in severe cases of the disease.

Gut-associated Bacteroides species were found in the lungs of 41% of acute respiratory syndrome patients compared with only 3.8% of healthy controls, and were also positively correlated with elevated levels of inflammatory markers in

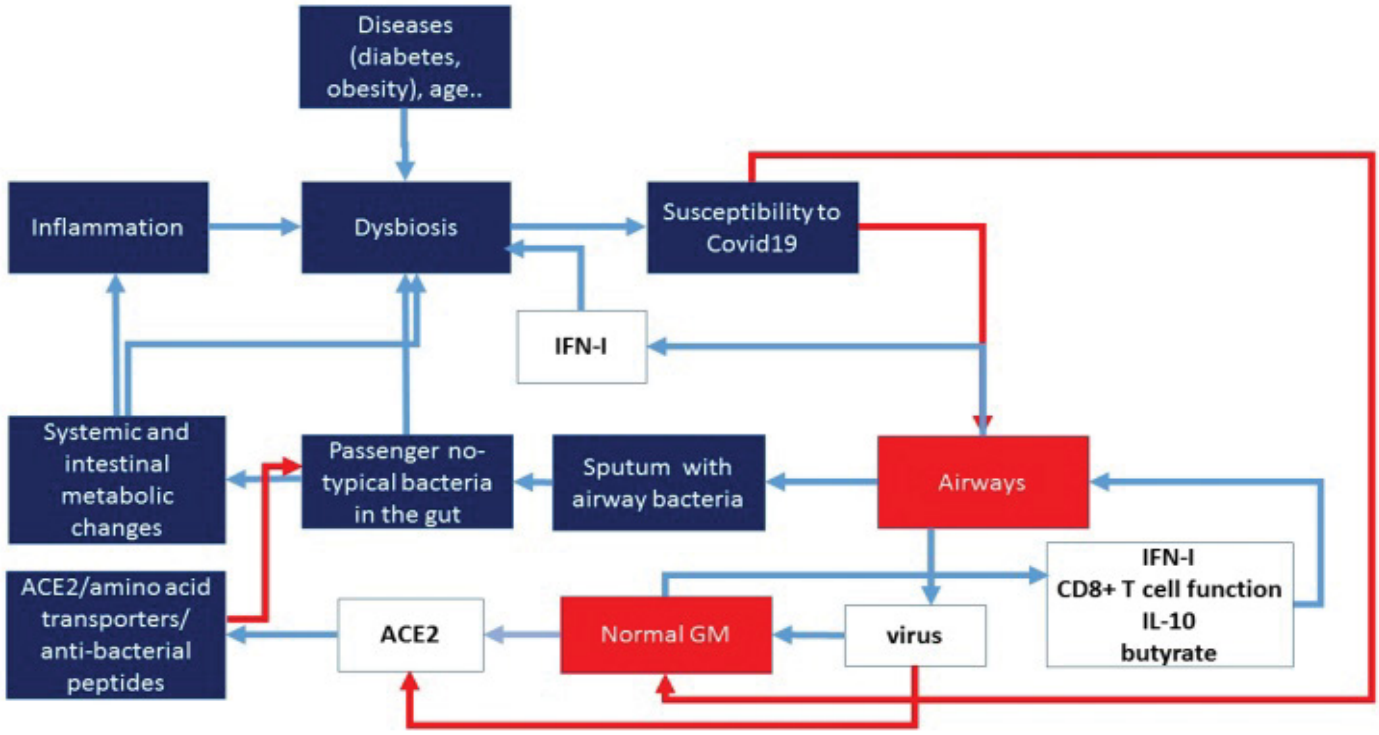

Figure 1. Factors involved in the crosstalk between viral infections and GM. ACE2 regulates the intestinal uptake of tryptophan, mediated by B(0)AT1. Tryptophan stimulates the secretion of antimicrobial peptides (AMPs) through the mTOR pathway. Antimicrobial peptides can influence the composition of the gut microbiota by inhibiting the propagation of nonresident microbiota (red ovals). Butyrate-producing bacteria (green ovals) stimulate macrophages, dendritic cells (IC-immune cells), and T cells, and the production of IFN-I and anti-inflammatory interleukins. SARS-CoV-2 (red circle) binds to ACE2 and inhibits the activity of the associated transporters, breaking the balance in microflora abundancies. ACE2, Angiotensin-converting enzyme 2; IFN-I, Type I interferon (IFN-α); B(O)AT1, Sodium-dependent neutral amino acid transporter; mTOR, The mammalian target of rapamycin.

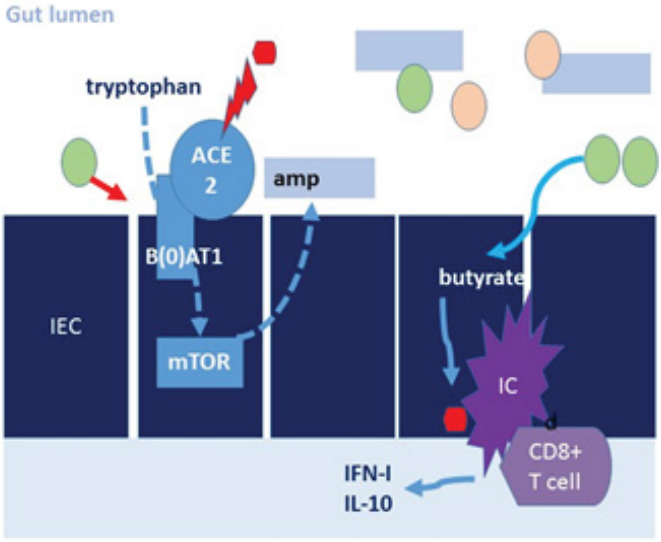

Figure 2. Role of the gut-lung axis in COVID-19. Red arrows represent suppression and blue arrows represent activation of downstream processes.

Table 1. Statements and evidences.

Main Statements, Evidence	References
Compositions of GM and lung commensal microbiomes correlate with systemic changes in a state of immune system	
GM influences immune response to respiratory viral infections (gut-lung axis).	[37,38]
A balance of the microbiota is necessary for homeostasis: a comprehensive study of immune system modulation by GM in mice.	[55]
Lung commensal microbiota critically regulates the generation of virus-specific CD4 and CD8 T-cells and antibody responses following respiratory influenza virus infection.	[36]
Gut-associated *Bacteroides* presence in lung positively correlates with elevated inflammatory markers in plasma.	[107]
GM composition changes in adenovirus and H1N1 infections.	[68-71]
Lung-infection derived CCR9+CD4+ T-cells can be recruited to the small intestine.	[88,89]
Influenza virus infection induces microbiota-mediated Th17 cell-dependent inflammation.	[88]
IFN-I molecules produced in the lung supported a depletion of obligate anaerobic bacteria and enrichment of Enterobacteriaceae in the gut.	[61]
GM composition and systemic immune markers correlate.	[49,50,71,36,62,73,75-83]
Microbiota signatures in the gut and respiratory system may predict severity and long-term outcomes in COVID-19 patients	
COVID-19 severity negatively correlates with Bacteroides, Firmicutes species abundancies.	[49,51-54,73,74]
COVID-19 severity positively correlates with *Coprobacillus, Clostridium ramosum, and Clostridium hathewayi* .	[56]
Negative correlations with *Faecalibacterium prausnitzii, Bacteroides* species.	[56]
Bacteroidesgenus, *Streptococcus genus* and *Clostridiales* order were negatively correlated with the inflammatory cytokines, *Ruminococcus genus*, *Blautiagenus* and *Lactobacillus genus* showed positive associations.	[49]
IL-2, IL-4, and IL-6 levels correlate with abundancies of *Finegoldia, Anaerococcus, Peptoniphilus, Intestinibacter, and Prevotella genera.*	[71]
GM may play a causative role in gut-lung axis	
GM modulates absorption of nutrients that may play a role in aetiology of systemic or organ pathologies.	[29- 31,32-35,57]
Microbial metabolites (short-chain FA, desaminotyrosine) regulate the immune system.	[49,58,64,65, 78,80-87]
GM modulates host's immune system.	[49,60-66]
GM effects ACE2 expression in the gut.	[90,97,98]
Intestinal microflora disorders reduce host antiviral immune response.	[36,32-35]
Changes in GM composition may effect viral infection outcome	
Immune system modulation is an intermediate step in the gut-lung axis	[60-66]
Nutrient absorption and intestinal microflora disorders reduce host antiviral immune response.	[29- 31,32-35,36]
Immune system modulations in viral pneumonia correlate with the GM composition.	[36,49,62]
Bifidobacterium breve positively modulates an outcome of viral pneumonia.	[65]
dysbiosys causes changes in intestinal permeability and endotoxin intoxication.	[64,65]
GM composition shifts are linked to hiperinflammatory response.	[49]
Influenza-specific CD8+ T-cell function and Type I interferon (IFN-I) signalling in macrophages are associated with GM signalling.	[49,62,65,78,85-88]
IL18, IGA levels can be affected by GM Furmicutes abundancies.	[49,75]
Microbial metabolites regulate immune system.	[49,64,80-83]
IL-2, IL-4, and IL-6 systemic levels correlate to *Finegoldia, Anaerococcus, Peptoniphilus, Intestinibacter, and Prevotella* abundancies	[71]
ACE receptors expression is influenced by GM and, in their turn, influence GM composition	[90,97,98]
Pre- and probiotics therapies may be complementary to vaccines, treatment, and during patients' rehabilitation	
Richness of GM composition is decreased in pathologies associated with a viral infection severity.	[3,37,38,48,49]

Immune system can be modulated via balancing a GM composition.	[60-66,85]
High fibre diet supports positive outcome in viral pneumonia.	[36,62]
GM-produced metabolites modulate anti-viral immune response.	[58,62-65,78,80-87]
Bifidobacterium breve supplementation positively modulates an outcome of viral pneumonia.	[66]

plasma [107]. The relative abundances of opportunistic pathogens such as *Streptococcus*, *Rothia*, *Veillonella*, *Erysipelatoclostridium*, and *Actinomyces*, were also increased in the lungs of COVID-19 patients. Among these, *Rothia* is already known to contribute to the pathogenesis of pneumonia, especially in immune compromised individuals [108]. *Streptococcus* and *Rothia* were also associated with susceptibility to secondary bacterial lung infection in patients with avian H7N9 virus infection [109], and the opportunistic pathogens *Prevotella*, *Finegoldia*, and *Peptoniphilus*, were enriched in lung microbiomes of H1N1 patients [60,71].

Discussion

The severity of COVID-19 is associated with gastrointestinal symptoms [39,40,45], and we can suggest with high confidence that the digestive tract may be a site for virus replication and activity [43-47].

Prolonged diarrhea in COVID-19 patients is negatively correlated with gut microbiota richness and composition [48,49] and positively correlated with markers of ongoing inflammation [50]. Such associations are typical of dysbiosis, and dysbiosis is typical in diabetes, obesity, and autoimmune and aging-related diseases, which are comorbidities associated with severe COVID-19 outcomes [13,51-54]. Modulation of some of the listed diseases by pre- and probiotics has already been considered and shown to be successful [7,9,16,19-21,31,51-54]. We suggest that a similar approach may be effective with respect to prophylactic, and treatment of COVID-19 and other viral diseases [36-38,62, 66,90,96] as well as along the vaccination [110].

Alterations in Bacteroidetes and Firmicutes [28,49,51-54,71,74] taxa were the most common in severe COVID-19 cases, with an increase in the abundance of species relying on their own basic nucleotide and amino acid biosynthesis and glycolysis, and a decrease in the abundance of short-fatty acid producers [56–59]. The latter are also known to possess anti-inflammatory properties [60-66,71,78, 81-87], and modulate ACE2 receptor expression and amino acids metabolism (Figure 1) in the gut lining [49,55,97,98]. Thus, fiber-based diets, butyrate-rich fermented products, enrichment of a diet for particular cofactors involved in butyrate-generating pathways, and decreased sugar intake would play beneficial roles in GM-led protection from inflammation. ACE2 and its inhibitors have been explored as potential targets [90,97] and targeting of amino acid transport and biosynthesis in bacteria or amino acid supplementation in the host [49,97] can be also considered.

Changes in the composition of GM may result in loss of antiviral resistance and respiratory system complications [55,83,85,87]. However, respiratory viral infections may also lead to changes in GM composition [89,90] (Figure 2). Interesting correlation data [36,51-59,68-71,75] suggest that a link exists between the niches (gut-lung and gut-immune system); however, the causative vectors of most observed correlations have not yet been defined. We propose that the complex system of cross-regulation in the case of GM-led pathology (Figure 2) may be modulated by careful targeting of immune components (such as proinflammatory interleukins, for instance). The main evidence supporting our statement has been collated and presented in Table 1 for evaluation.

Conclusion

We believe that further understanding of the physiological impact of the ‘gut-lung axis’ may help in the development of better prophylactic and intervention strategies for COVID-19 and other diseases caused by respiratory viruses. The dysbiosis manifestation and microbiota signatures in the gut and respiratory system, associated with higher mortality risk and long-term outcomes in COVID-19 patients, may be used in health monitoring during and after epidemics and be addressed by new pre- and probiotics therapies.

Conflict of Interest

There are no conflicts of interest associated with this publication.

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