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REVIEW ARTICLE

COVID-19 and Gut Microbiota: A Potential Connection

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Abstract Currently, world is facing a global outbreak causing a pandemic threat known as COVID-19. This infectious disease is triggered by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Gut microbiota harbours multi species community with a strong impact on host immune homeostasis. However, our knowledge about this gut microbiota and its symbiotic relationship with immune activation in association with SARS-CoV-2 is limited. Unbalanced bacterial flora with too many opportunistic infections can shift immune system towards a cascade of inflammatory responses leading to multi organ damage. This review will highlight immune-regulation via various mechanisms in SARS-CoV-2 infection. Diet has an unbelievable influence on gut microbiome that allows a new state of homeostasis to be reached through timing, frequency and duration of intake. This review article focuses on gut, lung microbiota and immunomodulation with specific attention on immune activation by gut microbiota.

Keywords SARS-CoV-2 · Immune system · Microbiota · Probiotic

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Introduction

Human gastrointestinal (GI) tract is home to intricate community of commensal bacteria called as gut microbiota. The number of microorganisms found in GI tract has been predicted to exceed 10^{14}, which consists of 100 times the amount of genomic content (microbiome) as the human genome [1]. Gut microbiome contains 1000–1500 species of bacteria with an individual containing approximately 160 species depending upon the environmental and genetic factors. Firmicutes and Bacteroidetes are predominant in gut while Proteobacteria, Bacteroidetes and Firmicutes preponderate in the lung [2].Over the passage of time, gut microbiota has been providing numerous benefits to its host which includes inhibition of pathogens directly, maintaining gut integrity, metabolizing undigested compounds especially certain carbohydrates and development of tolerant mucosal barrier and intestinal epithelium. [3] Complex interplay and alliance between immune system and gut microbiota regulates and supports each other as 70–80% of the total body's immune cells are present in the gut. Dysbiosis defined as changes in gut microbiota leading to microbial imbalance has not only been closely linked with the pathogenesis of many inflammatory diseases but plays a critical role in diverse infections as well. Viruses constitute one of the commonest invading pathogens triggering robust interactions between viruses and commensal microbiota. Patients with COVID -19 suffer from fever, cough, myalgia, fatigue and pneumonia which might aggravate to acute respiratory distress syndrome or multi organ dysfunction. [4] Various studies have found the presence of gastrointestinal symptoms during the course of disease which are nausea, vomiting, diarrhoea and abdominal pain. These symptoms might be either due to direct infection of the enterocytes by SARS-CoV-2 through

a phenomenon of ′gut lung axis′ involving the gut and the lung microbiome or through immunoregulatory mechanisms. [5] The purpose of this review is to summarize the knowledge available and possible links of gut microbiota in immunomodulation during SARS-CoV-2 infection.

Material and Methods

The source of this information is PubMed indexed research and review articles.

Microbiota, Gut Lung Axis and COVID-19 a Possible Link

The gut microbiota has been shown to affect the lung health via interactions between the lungs and the gut through a phenomenon called 'gut lung axis'. [6] Gut lung axis is a bidirectional tool i.e., the gut microbial metabolites, endotoxins can affect the lungs and vice-versa. [7] Some studies have demonstrated changes in the gut microbiota in mice during the respiratory viral infections like in case of the influenza virus or the Respiratory syncytial virus. [8] Proposed interactions between the systems during gut lung axis is made mainly by immune cells or the gut microbiota and its products. Microbiota and their products that enter the intestinal mucosa are phagocytosed by the antigen presenting cells leading their transfer to mesenteric lymph nodes which might stimulate B and T cells. Once activated, these cells might relocate to the original site i.e., intestinal mucosa or towards different site for instance, the lungs. Second proposed mechanism includes the transfer of surviving bacteria or bacterial products to the lungs by blood or the lymphatic system causing a general or local immunological response leading to further lungs damage. [9] (Fig. 1) Impact of gut microbiota towards lungs is shown in various studies like in case of mice lacking intestinal microbiota shows a lower pathogenic clearance in lungs [10]. It has been reported in a study that dosage of intratracheal Lipopolysaccharide (LPS) might disrupt the lung microbiota, which might in turn leads to disruption of gut microbiota with an increase in the bacterial load [11].

One of the major manifestations of COVID-19 is acute respiratory distress syndrome and pneumonia. Gut microbiota has also been relevant in pathogenesis of Acute respiratory distress syndrome (ARDS) and sepsis. [12] Shen et al. in his study analysed variations in the composition of the lung microbiota with respect to SARS-CoV-2-infected patients. He concluded that as compared to healthy controls, microbial composition in the bronchoalveolar lavage fluid (BALF) was different in infected patients. It was dominated by commensal bacteria commonly found in the oral and upper respiratory or pathogenic bacterial strains. He also emphasized that patients with community-acquired pneumonia had similar microbial composition. [13]. A study was conducted highlighting the alterations in gut microbiota with respect to SARS COVID and H. Influenza infection. [14] This cross-sectional study constituted of 30 patients with COVID-19, 24 patients with influenza A(H1N1), and 30 matched healthy controls (HCs). Further, 16S ribosomal RNA gene V3–V4 region sequencing was used to recognize differences in the gut microbiota. Results showed that HINI patients displayed lower diversity and different overall microbial composition compared with COVID-19 patients. On comparison with healthy controls, COVID-19 patients had higher relative abundance of opportunistic pathogens, such as Streptococcus, Rothia, significantly reduced bacterial diversity and a lower relative abundance of advantageous symbionts. This study also suggests the potential value of the gut microbiota as a diagnostic biomarker for COVID-19. [14].

Many reports have stated the presence of gastrointestinal symptoms throughout the course of the disease [15–17] as well as the existence of viral RNA in the faecal specimen. [16, 18] There also has been a pilot study conducted which provides evidence for prolonged 'quiescent' GI infection even in the absence of GI manifestation. In this study, seven (46.7%) of 15 patients with COVID-19 had stool positivity for SARS-CoV-2 by viral RNA metagenomic sequencing. Three patients continued to display active viral infection up to 6 days after clearance of SARS-CoV-2 from respiratory samples. Bacterial species like Collinsella aerofaciens, Collinsella tanakaei, Streptococcus infantis, Morganella morganii were present in large numbers in faecal samples with high SARS-CoV-2 infectivity and also higher functional capacity for nucleotide de novo biosynthesis, amino acid biosynthesis and glycolysis. On the other hand, short-chain fatty acid producing bacteria like Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii and Lachnospiraceae bacterium 1_1_57FAA had low to no SARS-CoV-2 infectivity. [19].

Presence of transmembrane protease serine-2 (TMPRSS-2) and Angiotensin Converting Enzyme-2 (ACE-2) receptor have been reported in the enterocytes from the colon and ileum which are required by SARS-CoV-2 to enter and infect the cells. [20, 21] There is a possibility that these gastrointestinal symptoms mighty be due to infection of SARS-CoV-2 in the enterocytes. [22] It can also be speculated about the phenomenon of gut lung axis where these gastrointestinal changes in COVID-19 might be a secondary effect of the major pulmonary changes; or the SARS-CoV-2 might be infecting the enterocytes which might lead to gut dysbiosis and might cause an increased damage to the lungs. Elderly individuals usually have less oriented gut microbiome. [23] COVID-19

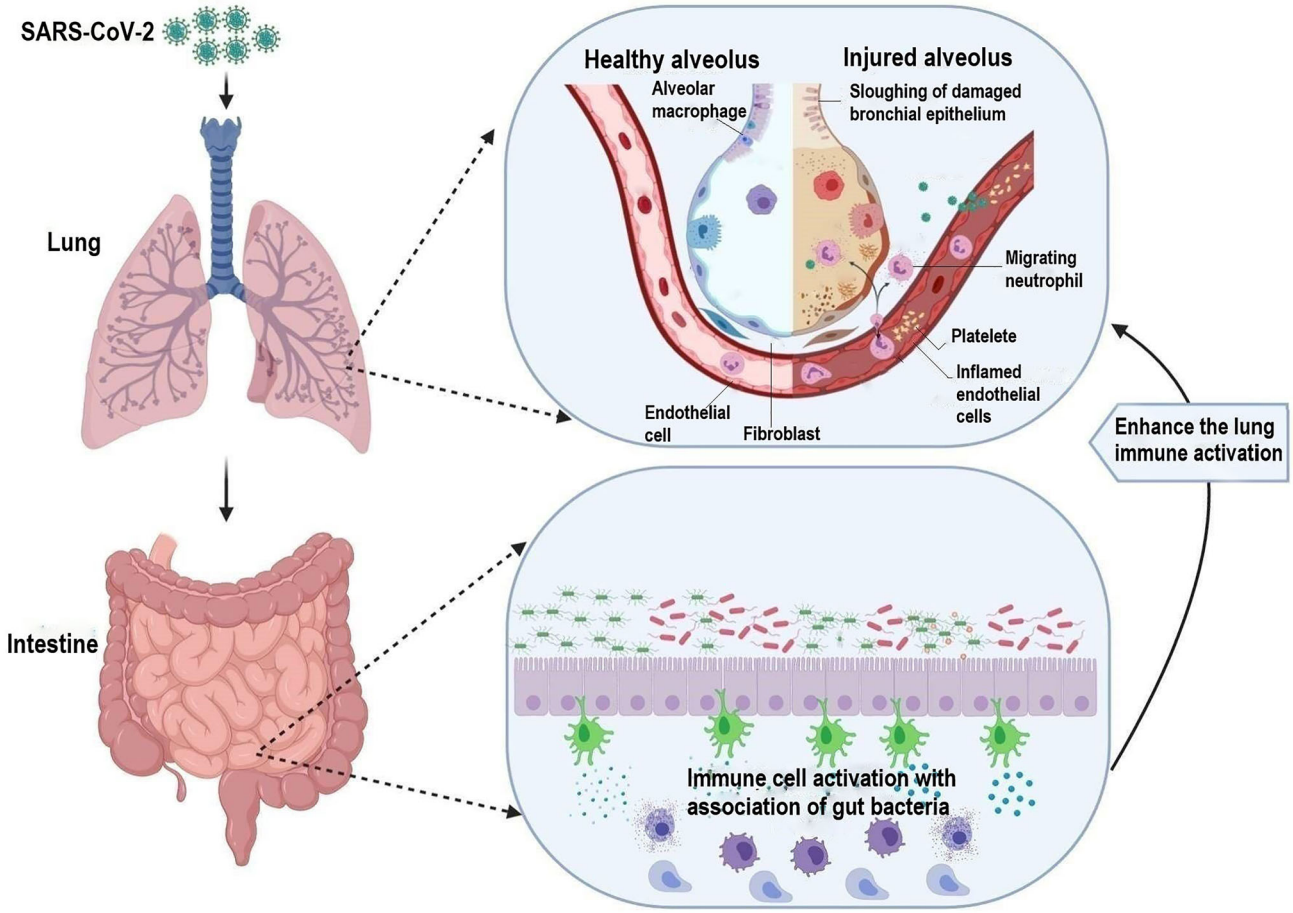


Fig. 1 Shows the gut lung axis. Gut microbiota activates the immune cells enhancing the lung immune activation

inclination towards more severity in elderly might also show a link between a less diverse microbiota and the infection of COVID-19. But this speculation requires a further research and clinical trials.

Gut Microbiota, Immunity and COVID -19

Gut microbiota is associated in pathogenesis of various diseases like inflammatory bowel syndrome (IBD), chronic kidney disease, type 2 diabetes, cardiovascular disease. [7, 24]. Human intestine harbours an extraordinary mechanism for development of the host immune system. Intestinal homeostasis is achieved by the interaction and coordination of the intestinal innate and adaptive immunity with mutual beneficial relationship between the two. Regulation of innate immunity via the gut microbiota is done using various types of cells mainly the antigen presenting cells consisting of dendritic cells in the Peyer's patches in the intestine, Langerhans cells and macrophages. [25] These cells have some tolerant immunogenic properties towards the gut microbiome, as in case of macrophages there is development of ′inflammation anergy′ [25, 26]. Other cells in the innate system that interacts with the gut microbiome are the mast cells and Natural Killer (NK). A study has shown that the mouse gut microbiota played an essential role in enhancing production of IL-22 producing NKp46 cells [27]. The interaction of gut microbiota by adaptive response consists mainly involvement of 2 types of cells, B and T lymphocytes. B cells associated with the gut are found usually in the payer's patches. Gut microbiome may also contribute to development of plasma cells as, a study in germ free mice has revealed lower levels of plasma cells. [28] T cells also play a pivotal role in the adaptive system. After activation CD4 + T cells can differentiate into 4 classes Th2, Th1, Treg (regulatory t cells) cells and Th17. [25] The immune homeostasis in gut which might affect the lungs as well by the gut lung axis is a balance between the pro-inflammatory responses maintained by Th17 cells and T regulatory cells which constitutes the anti-inflammatory response. [7] Studies have reported that gut microbial interactions might induce various cells in immune response like *Bacteroides fragilis* in the gut might induce the formation of the Th1 cells, *Clostridia* might induce the regulatory T cells and

segmental filamentous bacteria induces the Th17 cells. [29–32] The microbial metabolic process affects the production of cytokines in the gut as in case of influenza virus infection where microbiome affects the interferon signalling and increases the production of chronic phase protein. One hypothesis state that COVID-19 interaction with microbiome might affect the cytokine production and may even lead to over production of pro-inflammatory cytokines. [33] Some cytokines like IFNγ, MCP-1, IP10, and IL1B are elevated which might show higher activity of Th1 cells, as previously stated that gut microbiota also interacts with the immune cells. [30] So, there is a possibility of COVID-19 interaction with gut microbes which might lead to higher induction of the immune cells. (Fig. 2) Other impact of gut microbiota includes release of immunomodulatory signals and metabolites like antimicrobial peptides, polyamines, short chain fatty acids which help in regulating the immune system. [34] As seen in *Bifidobacterium lactis*, a probiotic strain has shown to increase the production of NK cells, mononuclear leukocytes, CD4 + and CD25 + T cells. [35] To summarize, the gut microbiota has a greater role in host immunity and SARS-CoV-2 might be interacting with gut microbiome and might be infecting the enterocytes to induce the gastrointestinal symptoms.

Dysbiosis and COVID-19

Balanced gut microbiota implies an increased effectiveness towards the lung immunity [9], as seen in a germ-free mouse which had a lower lung pathogen clearance. [7] Viral infections might also lead disturbance in the gut microbiota as seen in case of infection by the influenza virus in mice which lead to increase in *Enterobacteriaceae* in lungs and reduced the *Lactococci* and *Lactobacilli* in the microbiome of intestine. [7] Many multifactorial diseases have been shown to be linked with intestinal dysbiosis including autoimmune, metabolic, inflammatory neurodegenerative and neoplastic diseases. Innate and adaptive immunity control the colonization of the intestinal microbiota through mechanisms including the production of antimicrobial peptides and IgA antibodies. A dysbiotic microbiota may actively influence its colonization n by altering the functions of innate and adaptive intestinal immunity. Dysbiosis has been associated with many immune-related human diseases, but in many cases, it remains to be established whether dysbiosis is a cause or consequence of the disease. [36] A small report from china revealed gut dysbiosis in COVID-19 patients with lower levels of *Bifidobacterium* and *Lactobacillus* both of which are considered to be probiotic strains. [37] One study highlighted downregulation of ACE2 receptors expression in SARS patients during infection. [38] Expression of the amino acid transporter B0AT1, which controls the intestinal uptake of tryptophan is regulated by ACE2. [39] The mRNA expression of antimicrobial peptides through the mTOR pathway is regulated by tryptophan [40], and antimicrobial peptides may influence the composition of the gut microbiota. [41] As a result, intestinal absorption of tryptophan is decreased due to ACE2 downregulation and reduces the secretion of antimicrobial peptides, leading to increased pathogen survival and gut dysbiosis (Fig. 3).

A pilot study was also performed which examined shotgun metagenomic analysis of faecal samples in 15 patients of COVID-19 and found that the patients had major changes in the faecal microbiome in contrast to controls. They also found a decrease in beneficial commensals organisms and an increase in the opportunistic pathogens. Even after waning off respiratory symptoms and clearance of SARS-CoV-2 in throat swabs, lower levels of symbiotic organisms and gut dysbiosis persisted. Study also found that at baseline, 23 taxa of bacteria were found to be associated with COVID-19 severity majorly belonging to *Firmicutes* phylum (15 of the 23). 8 out of 15 showed the positive correlation and 7 of them showed a negative correlation with the disease. Genus *Coprobacillus*, the species *Clostridium hathewayi* and *Clostridium ramosum* are the major bacterial groups which are positively correlated with the severity of disease. Both of the clostridia species are associated with the bacteremia and human infections [42–44] and *Coprobacillus* is shown to up-regulate the ACE-2 receptor. [45] *Faecalibacterium prausnitzii* and *Alistipes onderdonkii* have been shown to have a negative correlation with COVID-19 severity according to the above described study. *Alistipe*s are involved in maintaining gut immune homeostasis, while *Faecalibacteriump rausnitzii* is considered to have anti-inflammatory properties which might be required due to presence of a high inflammatory response during COVID-19. During the duration of the disease and over the period of hospitalization they found that across all the faecal samples, 14 bacterial species were associated with the faecal viral load in SARS-CoV-2 individuals. Among them, *Bacteroides thetaiotaomicron, Bacteroides dorei, Bacteroides ovatus and Bacteroides massiliensis* showed significant negative correlation with faecal SARS-CoV-2 specimen load [42], and all of these are associated with the decrease of ACE-2 expression in the colon. [45].

As above study shows that various species are up-regulated which might be involved in higher expression of ACE-2 or the other species are down regulated which negatively controls the ACE-2 expression in the COVID-19 infected individuals. There is also a decrease in species involved in immune homeostasis and inflammatory response which are both required in maintaining the COVID-19 infection in the body. So gut dysbiosis might be

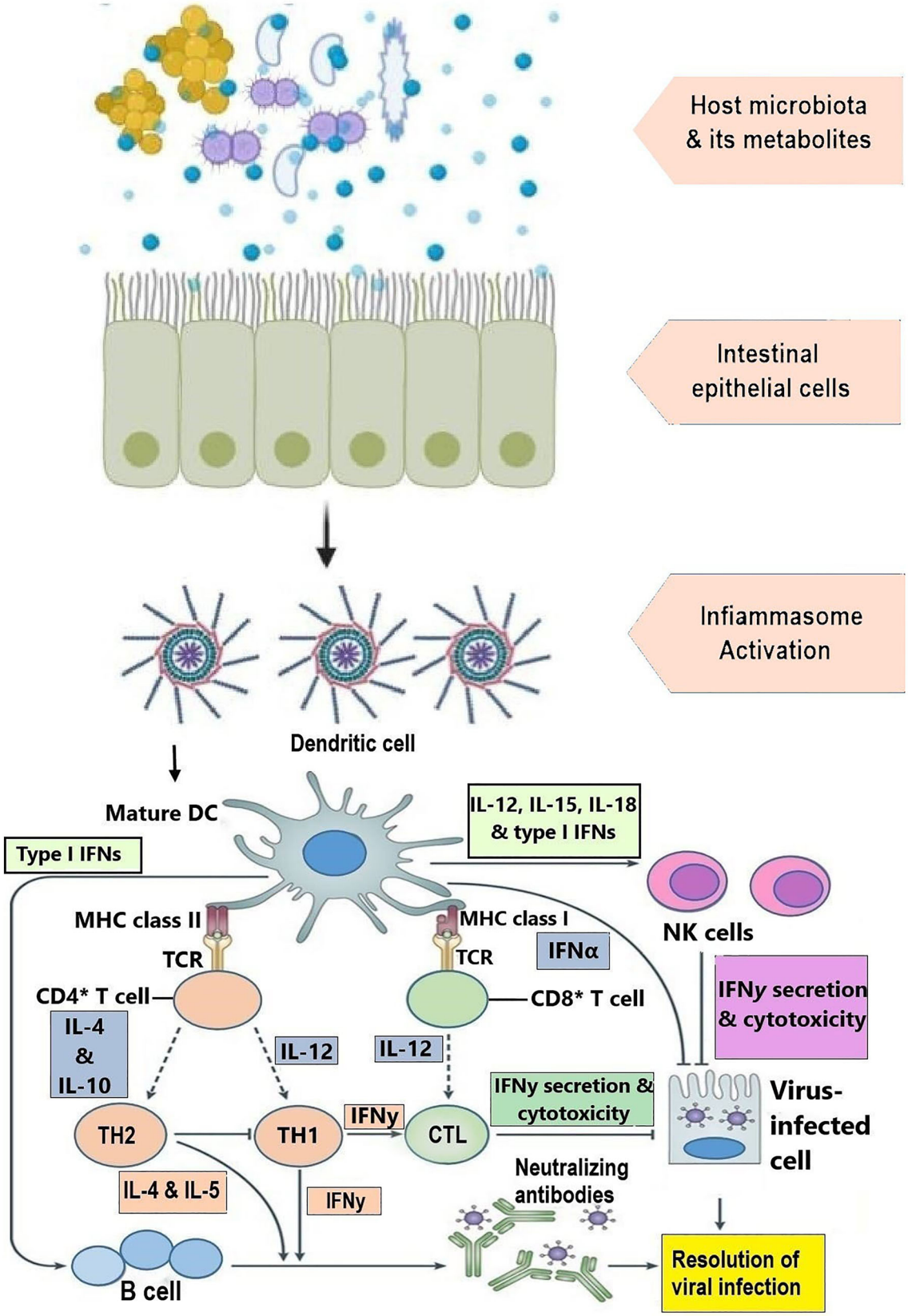


Fig. 2 Shows the role of gut microbiota in triggering cascade of inflammatory reactions in response to the SARS-CoV- 2 leading to resolution of viral infection

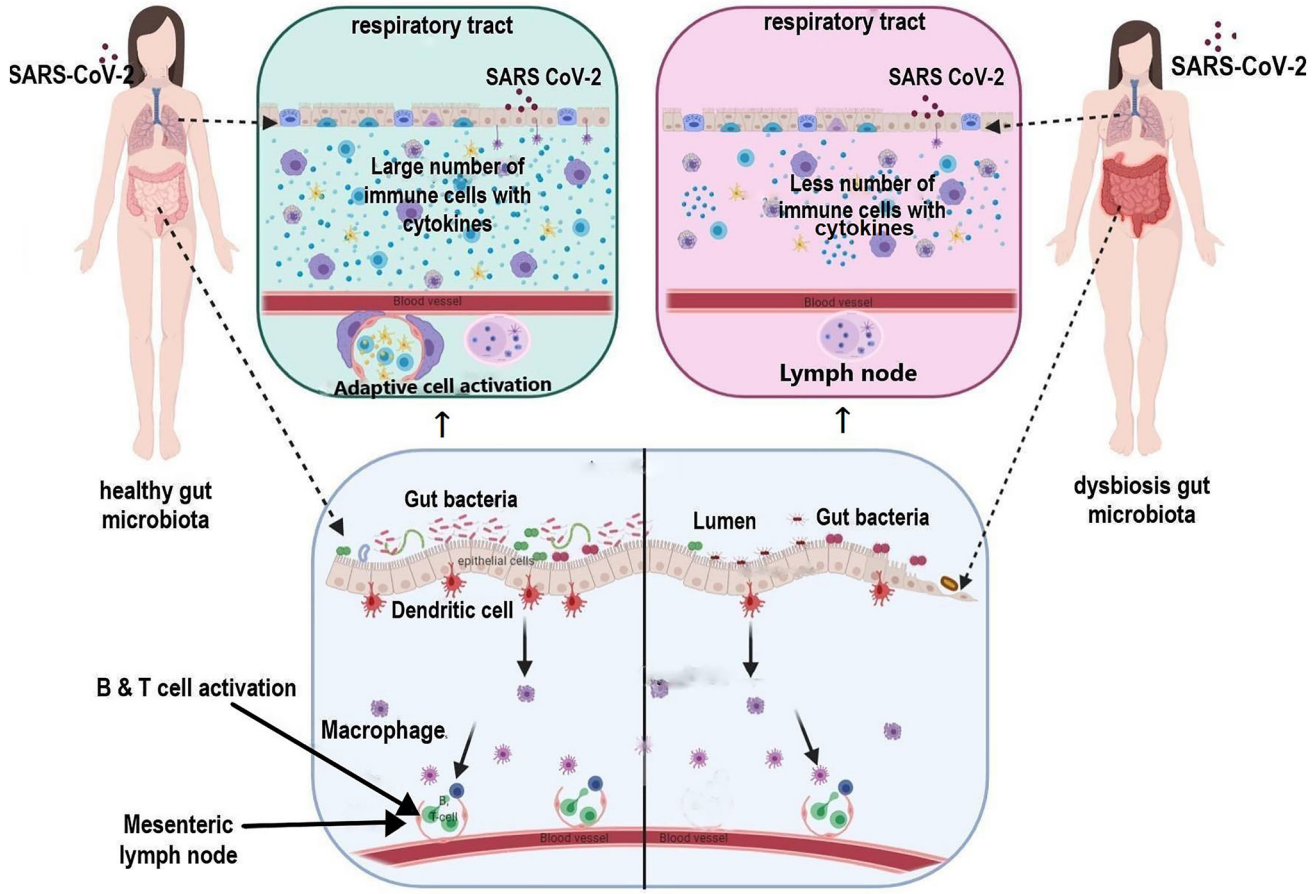


Fig. 3 Shows that how the healthy gut microbiota is able to control the lung infection by SARS-CoV-2 by producing large number of immune cells as compared to a smaller number of immune cells by dysbiosis in gut microbiota

associated in higher severity of COVID-19 as compared to the normal individuals. Another study which analyzed 30 patients also reported a decrease in bacterial diversity, a higher rate of increase in opportunistic pathogens such *as Actinomyces, Rothia, Sterptococcus and Veillonllea*, as well as a decerase in beneficial organisms in patients suffering from SARS-Cov-2 [14].

Currently, it is speculated that SARS-Cov-2 might also be associated with gastrointestinal symptomps like diarrhoea, vomiting, nausea and abdominal discomformt. ACE-2 receptor which is required by the SARS-CoV-2 to enter the host cells [20], its expression might be modulated by the gut microbiome. As seen in a study with mice model–showed a decerase in colonic ACE-2 receptors with the induction of gut microbiota in GFC (conventionalized GF) rats than in GF (Gerem free) rats [46].

Gut Microbiota, Diet, and COVID-19

As dysbiosis might be an essential factor in disease severity during COVID-19, maintaining a healthy gut is essential during this pandemic. Diet with low-fibre and high fat/carbohydrate are usually responsible for gut dysbiosis, [47] and this change in homeostasis might be responsible for an altered immune response. In a study in mice with high fibre diet which was seen to have high levels of circulating short chain fatty acids is said to have protective action against allergic inflammation in lungs. Thus, a fibre rich diet might not only affect the individual's gut microbiota but also affect the lung microbiota, showing an effect of nutrition over the lung immunity. [48].

The gut microbiota can rapidly respond to acute exposures as well as long term effects of diet. It displays a high interindividual day to day variability and has high ability to double themselves within an hour. [49] Histone acetylation through epithelial histone deacetylase 3 (HDAC3) has been closely associated with variations in gut microbiota. This HDAC3 integrates with the circadian clock which affects the nutrient intake through the metabolic gene expression. This interaction also regulates lipid intake leading to diet induces obesity. [50, 51] Night shift workers having disrupted sleep patterns, undergo an altered and disturbed gut microbiome leading to increase in dietary intake. It has also been brought into notice that metabolic stress is induced

due to rise in an inflammatory response. [52] The feeding regimen, feeding time, duration and frequency has a great influence on gut microbial composition, function and host health. The fact that time of eating was related to the presence of several bacteria was reported by Kaczmarek et al. [53]. Similarly, Thaiss et al. in mice models showed that rhythmic food intake not only increases microbial abundance but also leads to 15% fluctuations in commensal bacteria in the day. [54] Impact of meal timing in humans on gut microbiota was reported by Collado et al. in 2018 randomised crossover study. [55] This study concluded that salivary microbial profile gets altered as a result of taking late meal (at 17:30 in place of 14:30). It has been shown that salivary taxa when increased affect basal metabolic rate, body weight, glucose tolerance, body temperature and cortisol rhythm. [55], An individual's diet shows a cyclical seasonal pattern throughout the year due to seasonal availability and dietary likings. Overall dietary habits have a greater impact on influencing gut microbial environment and therefore microbial composition rather than day to day variations. [56] First three years of life have the greatest impact on microbial environment with respect to diet along with other factors. [57] More stable and adult-like microbial environment is established with greater resistance to infection by three years of age. Six to twelve-year olds in comparison to healthy adults show much greater microbial biodiversity [58]. Hollister et al., in his cross-sectional study also showed that in comparison to adults, pre-adolescent children had greater dietary diversity. They also showed that adults have a habitual established dietary pattern based on lifestyle and accessibility to food whereas children have a higher aptitude of exploring new foods. [58, 59] Despite this difference, amount of nutrient and its quality may still impact the gut microbiota. Healthy balanced diet, rich in cereals, whole grains, legumes, fruits and vegetables is advised to COVID 19 patients who are asymptomatic or patients with mild symptoms or in quarantine. The inverse correlation between the consumption of dietary fibre and the serum levels of C-reactive protein, Interleukin (IL)-6, IL-18 and tumour necrosis factor-alpha (TNFα) which are strong inflammatory cytokines is the main reason behind emphasising this kind of diet. Lower glucose concentrations and higher plasma concentrations of adiponectin, an insulin sensitising adipocytokine with anti-inflammatory properties are also noticed with high fibre diets. [60].

Probiotics are the non-pathogenic live organisms mainly found in the gastrointestinal tract. They are safe and can also be provided as food or dietary supplements. The major genera of probiotics in the gut are *Bifidobacterium, Lactobacillus* and *Saccharomyces* like *B. breve, B. longum*, *B. bifidum*, *L. reuteri, L. fermentum L. paracasei, L. rhamnosus.* Probiotics usually interact with various immune cells; therefore, they have a significant role in maintaining the immunogenic homeostasis mainly in the gastrointestinal tract. Other functions include maintaining the pH of the intestine and lowering the invasion and colonization by the pathogens. Probiotics are helpful against various diseases like *Clostridium difficile*–associated diarrhoea, antibiotic-associated diarrhoea, acute infectious diarrhoea, ulcerative colitis, hepatic encephalopathy, necrotizing enterocolitis, irritable bowel syndrome and functional gastrointestinal disorders. [61, 62] Studies have also reported that probiotic strains like *BifidobacteriumLactis, Bifidobacterium breve* and *Lactobacillus rhamnosus* show a good result in maintaining the innate immune system and the inflammatory response as seen in a mice-based study [7]. Chinese studies have showed that 58.71% of individuals suffering from COVID-19 were subjected to antibiotics, and 2–36% of these had diarrhoea. The use of probiotics has been suggested to lower susceptibility of the subsequent infection [63], even though probiotics have just satisfactory efficiency in treating the antibiotic induced diarrhoea. [64, 65] Studies have reported satisfactory effectiveness of probiotics towards viral induced respiratory illness. [66, 67] Use of probiotics in ventilator-associated pneumonia (VAP) is currently controversial but various studies and meta-analysis have found beneficial effect. [68] It has also been reported that probiotics (*Bacillus subtilis, Enterococcus faecalis* and *Lactobacillus rhamnosus* GG) were given to the individuals suffering from COVID-19 who were severely ill and ventilator ridden developed a less ventilator association as compared to placebo. [69, 70] Angiotensin 2 is also involved in bronchoconstriction, pulmonary hypertension, and pulmonary fibrosis. Probiotics might also influence the ACE-2 receptors as some microbial fermentation produces ACE inhinhitory peptides which will lead to lower production of angiotensin 2. [71].

Use of prebiotics can also be considered as prebiotics like maize fibre, inulin, polydextrose are known to improve the gut diversity, digestion and immunity especially in elderly individuals. Prebiotics have also shown to regulate various pro and anti- inflammatory cytokines [7] like carbohydrates present in whole grain are known to reduce the levels of IL-6 (pro-inflammatory cytokines) [54] and butylated high amylose maize starch is shown to increase the levels of IL-10 (anti-inflammatory cytokine). [55] This shows that prebiotics can have an immunogenic role in COVID 19. The prebiotics and dietary fibres are known to increase the production of short chain fatty acids and help in modulating the gastrointestinal lymphoid tissue and secondary lymphoid tissues. [56] The mechanisms of probiotics' antiviral effects are still unclear. Possible mechanisms, among others are suppression of virus replication hindering the adsorption, blocking the virus-cell

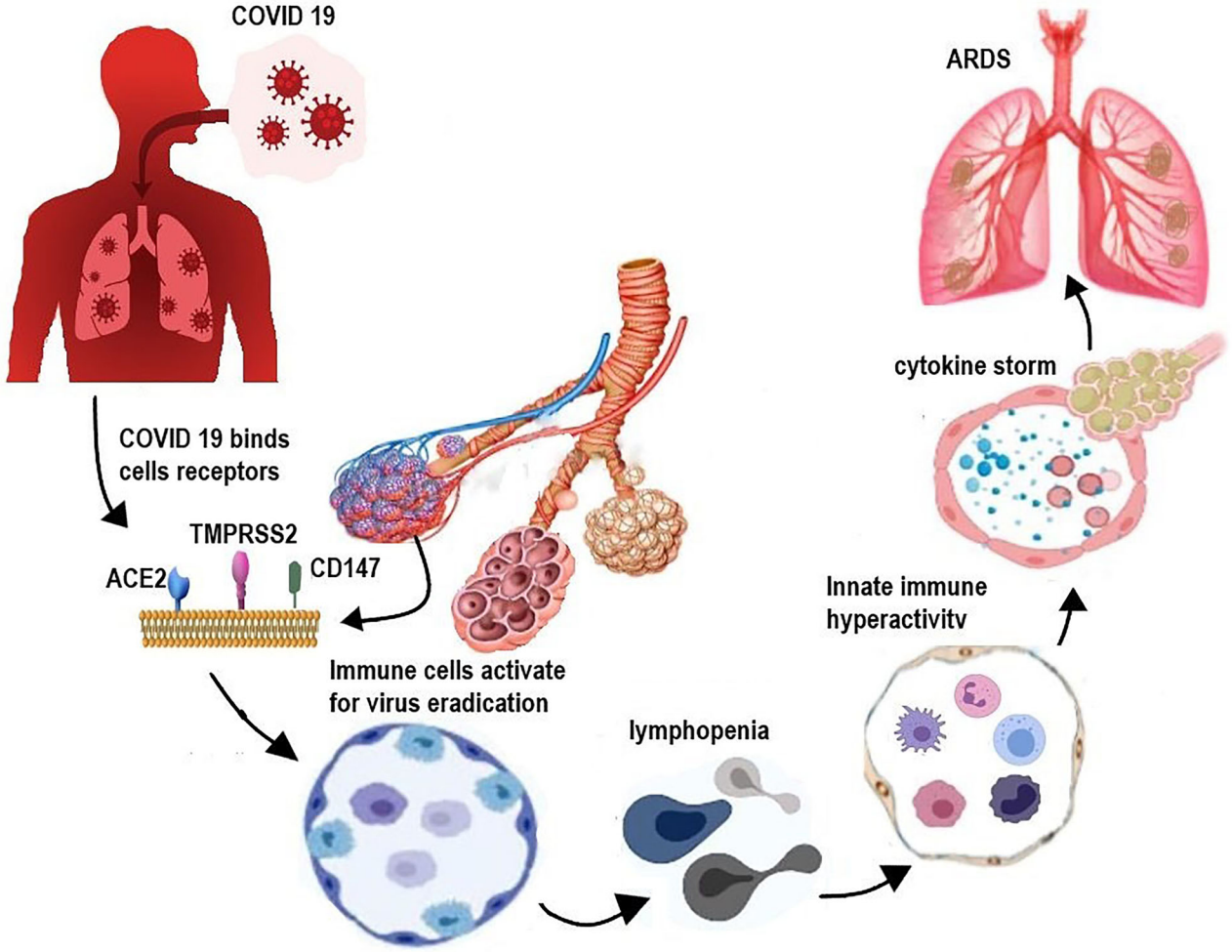


Fig. 4 Shows the series of events that might be responsible for an increased damage to the lungs causing immunological imbalance without involvement of gut microbiota

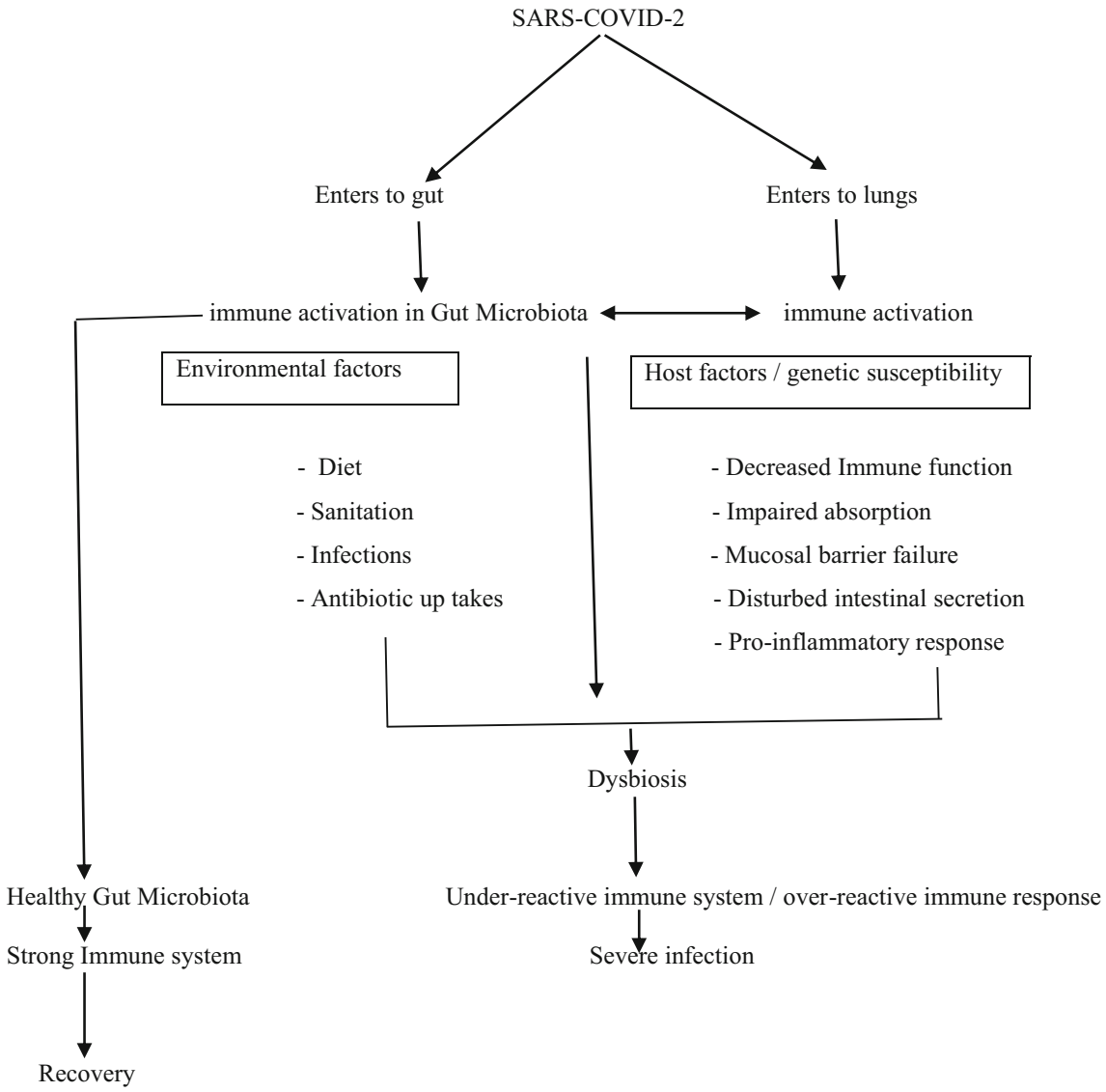
internalization process, binding to and blocking further infections, and, which is associated with ACE2. [72].

Lung, Immunity and COVID -19

The pathogenicity of SARS-CoV-2 is highly complex. It requires ACE-2 and TMPRSS-2 to enter the host cells. [20] The pathogenicity and virulence are also associated with inflammasome activation by the virus which might activate the epithelial, endothelial and the macrophages leading to increase in pro-inflammatory cytokines and interleukins like IL-18, IL-1β (a mediator of lung inflammation), which might take part in the inflammation responsible for disease severity. Viral detection by toll like receptor (TLR) i.e., TLR9, TLR8, TLR7 and TLR3 which might activate NF-KB pathway which might lead to formation of pro-inflammatory cytokines. [73, 74] SARS-CoV-2 might also infect the human T cells with the help of CD147 protein, present on the surface of T lymphocytes which might reduce the total T cell concentration and decreasing the immune response. During the infection of SARS-CoV-2, lymphopenia is also observed. [73] A study where peripheral lymphocyte levels were evaluated using flow cytometry in 60 patients found lower levels of T cells, NK cells and B cells. [75] Biopsy of a patient with COVID-19 revealed an accumulation of mononuclear cells (likely monocytes and T cells) in the lungs, coupled with low levels of hyperactive T cells both CD4 + and CD8 + in the peripheral blood. [76] This might explain that SARS-CoV-2 might be affecting the T cells. Eosinopenia is also reported in various studies during the infection of COVID-19. [73] (Fig. 4) Cytokine storm is also common during the course of COVID-19(4). IL-7, IL-2, IL-10, IL-6, granulocyte-colony stimulating factor, macrophage inflammatory protein 1 alpha, MCP-1, TNFα and IP-10 are found to be elevated in COVID-19 patients. [2, 33] These might be responsible for an increased damage to the lungs and might even cause some inflammatory responses in the distal site

like gastrointestinal region which might explain the gastrointestinal symptoms in individuals suffering from COVID-19. [2].

Influence of dysfunctional mitochondria on the immune response have been highlighted by many studies. According to a recent study, COVID 19 infected cases displayed an increased production of pro-inflammatory cytokines (CXCL-8, IL-6, CCL20, CCL3, CCL4 and IL-12) in human alveolar epithelial cells with dysfunctional mitochondria. Reduced responsiveness to corticosteroids and impaired repair responses have also been noticed in these cells. [77] These findings highlight a potential impact of dysfunctional mitochondria on modulating immune responses by triggering positive feedback loop that causes alveolar tissue damage as seen in the case of COVID-19 severe form. Whenever chemoattractant such as CXCL-8 are upregulated, they promote neutrophil infiltration into the lung. This contributes to the generation of ROS and protease activation which further contributes to the damage of mitochondria. [77, 78] A study concluded protection against acute lung injury from bone marrow-derived stromal cells as a result of mitochondrial transfer. [79] Some studies also highlighted that mitochondria contents (spin-offs such as mtDNA) are released into the cytosol and extracellular environment. [80, 81] when severely damaged. Along with ROS production there is also upregulation of Ca2 + levels and release of mitochondrial DNA into the cytosol. [82, 83] Pro-inflammatory cytokines such as IL-1β are driven by activating NLRP3 inflammasomes and induces IL-6 production through inflammasome-independent transcriptional regulation [84–86]. These cytokines are hallmarks of COVID-19 disease severity.



Conclusion

This review summarizes the association and implications related to gut microbiota in correspondence to COVID-19 through immunomodulation. There are possibilities which suggest a relationship, either in the form of 'gut lung axis' where the gut microbiota might be affecting the lungs or in form of immunomodulatory signals released by the gut microbiome. Healthy gut microbiota can control the lung infection caused by SARS- CoV-2 by producing large number of immune cells as compared to a smaller number of immune cells by dysbiosis of gut microbiota. Diet probiotics and prebiotics are the key modulators in regulating gut microbial environment and might be helpful in maintaining the homeostasis of gut microbiome and might influence the SARS-CoV-2 infection. Currently, this review presents various hypothesis that might explain a potential role of gut microbiota in SARS-CoV-2 infection. These statements require a scientific validation through various studies on gut microbiota profile of SARS-CoV-2 patients for their justification.

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Compliance with Ethical Standards

Conflicts of interest The authors declare that they have no conflict of interest

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