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Review Article

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Gut Microbiota Dysbiosis and Its Impact On Immune Response In Covid-19 Patients : A Review

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Abstract

The new corona virus SARS-CoV-2 infection and the COVID-19 pandemic have turned into an inexorable global public health and economic disaster. The gut microbiota is a diverse bacteria population that live in the human intestines. The gut microbiota plays important roles in the modulation of host metabolism and gene expression, epithelial integrity maintenance, and inflammatory and immune mediation. As a result, the normal gut microbiota plays a critical role in maintaining health and preventing disease.

The gut-lung axis is bidirectional, which implies that metabolites created from gut bacteria have an effect on the lung via blood, whereas lung inflammation alters gut microbiota levels. Lung dysfunction is caused by changes in the immunological responses of neutrophils, T cells, TLRs, and inflammatory cytokines such IL-1, IL-2, IL-10, IFN-, and TNF-, which all play a role in the severity of COVID-19. SARS-CoV-2 infects the lungs, triggering an immunological response in the gastrointestinal system and causing epithelial cell disruption in the lungs.

A growing body of evidence has recently emerged linking in gut microbiota dysbiosis to SARS-COV-2 infection. Hence, the modification of gut microbiota could be a possible therapeutic approach. Fecal microbiota transplantation (FMT) may improve the conditions of patients with SARS-COV-2 infection by manipulating the human intestinal bacteria. However, there is a scarcity of relevant research, and a significant amount of scientific study effort must be completed in the near future. In conclusion: Alterations of the intestinal flora play an important role in promoting the severity of COVID-19. Therefore, Careful attention to patients' intestinal microecology should provide a sound basis for the treatment for COVID-19.

Keywords: Covid-19, Gut Microbiota, Gut-Lung Axis, Immune Response

Introduction

The ongoing global pandemic of COVID-19 disease is characterized by active virus replication in the upper respiratory tract and is caused by a new coronavirus (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) [1]. As of August 2020, it had infected over 20 million individuals and killed 700,000 people over the planet [2]. It is enveloped, single-stranded, positive-sense RNA virus with a genome length of about 30,000 base pairs [3, 4]. Based on their genomes, they are divided into four genera: a, b, g, and d, with a- and b-coronaviruses infecting mammals [3].

In humans, mild upper respiratory tract infections, such as the common cold, have been reported to be caused by a-corona viruses. However, in the previous two decades, the world has seen three major outbreaks of highly lethal coronavirus illnesses in humans, notably COVID-19, which has turned into a pandemic of unprecedented proportions, straining global health care. More than 50 million cases have been reported globally as of December 20, 2020 (5). COVID-19 instances were first reported in Wuhan, China, in 2019 [4]. This disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a bat-borne b-coronavirus strain similar to SARS-CoV-1, the 2002 SARS outbreak's causal agent. SARS was a two-year outbreak that affected 29 countries and resulted in 8,096 illnesses and 774 deaths [6].

Another zoonotic coronavirus strain, SARS-CoV, was the cause

of the Middle East respiratory syndrome (MERS) outbreak in 2012, which spread to 27 countries and resulted in 858 deaths [6]. SARS-CoV-2 is suspected to have originated from bats because it is closely related to these strains [7]. COVID-19 has had a more harmful impact on the world than SARS or MERS due to its extreme contagiousness, which is estimated to be two to three times as severe than influenza [8]. COVID-19 case fatality rates vary greatly amongst nations, ranging from 1% to 15%; however, the rate is normally between 2% and 4% [9].

SARS-CoV-2 typically affects the respiratory system and can cause a wide range of symptoms, from minor illness to severe hypoxia owing to acute respiratory distress syndrome [10]. Fever, cough, myalgia, tiredness, and pneumonia are all common COVID-19 symptoms [4, 10]. There have also been reports of diarrhea, vomiting and nausea, indicating that the gastrointestinal (GI) tract is a source of infection [11-15]. A significant percentage of individuals tend to have identifiable gastrointestinal symptoms, albeit this percentage varies based on the patient groups evaluated [12, 16].

The digestive system is the body's largest immunological organ, and the microflora that lives there is thought to modulate host immune responses [17, 18]. We speculate that the occurrence of fever is linked to the host's immunological state and inflammatory response, which is triggered by dysbiosis of gut microbiota. For the development of new therapeutic remedies in the fight against this virus, a better knowledge of the pathophysiological relationship between gut microbiota modification and its impact on respiratory immune response is critical.

Host immunity and COVID-19 Infection

Despite mounting evidences on the immunological response to viruses, nothing is known about the precise immunologic mechanism of COVID-19 infections, and it is unclear whether activation of host immune responses is protective or harmful. A healthy balance of innate and adaptive immune responses can quickly manage the virus and eliminate infected particles from the body, but unbalanced immune responses can lead to viral spread, multi-organ failure, and high mortality [17]. As a result, further research into the immunological responses that occur during COVID-19, as well as the underlying cellular or molecular pathways, appears to be beneficial. Despite the fact that researchers are currently working on developing vaccines and testing antiviral medications in clinical trials, there are no effective prophylactic and clinical treatment options for COVID-19, yet [19].

Direct infection of the bronchi and bronchiole epithelium triggers the immune response against invading coronavirus. First, antigen-independent innate immunity serves as a first line of protection for leukocytes against microbes. Several cell types participate in innate immune defense, including neutrophils, eosinophils, basophils, monocytes, macrophages, lung epithelial cells, mast cells, and natural killer (NK) cells [20].

The innate immune cells express pathogen-recognition receptors (PRRs) to sense pathogen-associated molecular pattern (PAMP) that include C-type lectin receptors, NOD-like receptors (NLRs), RIG-I-like receptors (RLRs) and Toll-like receptors (TLRs) [21, 22]. RNA viruses, such as coronavirus, are recognized by cytosolic and endosomal RNA sensors, including RIG-I and TLRs (TLR2, TLR3 and TLR7), respectively [23-25]. It is demonstrated that the activation of TLR3 with the polyinosinic-polycytidylic acid (poly I: C) can inhibits infection related-coronavirus [26]. TLRs and RIG-1 recognize RNA viruses, which activate transcription factors such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and interferon regulatory factor 3 (IRF3), which then translocate into the nucleus and induce the expression of pro-inflammatory cytokines, chemokines, and type I interferon [27].

Type 1 INF is considered to be the first antiviral defensive line. Type I IFNs via IFNα/β receptor (IFNAR) activates the janus kinase (JAK), signal transducer and activator of transcription (STAT) signaling pathway(28). JAK1 and TYK2 phosphorylate STAT1 and STAT2 molecules in response to IFNAR signaling, forming a complex with interferon regulatory factor (IRF) 9. These complexes were injected into the nucleus to induce IFN-stimulated genes (ISGs) transcription and, as a result, antiviral protein production(6). Several ISG products, notably IFN-induced transmembrane (IFITMs) proteins 1, 2, and 3, inhibit SARS-CoV infection [29].

Furthermore, granulocyte colony stimulating factor, IP-10, TNF-, MIP-1, and MCP-1 levels were all higher in severe COVID-19 cases (30). COVID-19 is classified as a cytokine storm-mediated disease based on these laboratory data, which imply that an increase in pro-inflammatory cytokines is linked to disease development, severity, and death (31). To start this complex process, a stimulus such as microbial pathogen damages the barrier sites such as lungs or gut [32]. Currently, a large number of studies on the gut-lung axis revealed that alteration of gut microbiota play a key role in induction and furthering the progression of SARS-COV-2 infection [33-37].

The gut microbiota regulates immune responses in a variety of ways, including promoting the production of pro-inflammatory cytokines such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-), and interferon gamma (IFN-), favoring the generation of regulatory CD4+ T cells, and leading to the diversification of the B-cell repertoire and the production of T cell-dependent and -independent antibodies [38-40]. IL-6 is one of the most prominent cytokines in the inflammatory storm in COVID-19 patients (41) meanwhile, it is also the most essential mediator in the development of fever (42). Various studies have revealed that the gut microbiota is associated with disease severity, and several cytokines and inflammatory markers in COVID-19 patients [2, 33].

It also implies a novel treatment strategy for patients infected

with SARS-CoV-2 [43]. In fact, fecal microbiota transplantation (FMT), in addition to standard antiviral, has been shown to be effective in decreased fever and pneumonia exacerbation [44]. Therefore, the occurrence and severity of COVID-19 depends not only invasion path of the SARS-COV-2, virulence, immune system and viral load, but also on the GM stability as well.

Gut Microbiota

The gut microbiota (GM) is a diverse ecosystem that consists of a distinct array of bacteria and other microorganisms that work together in a symbiotic relationship. From an immunological perspective, microorganisms are viewed as pathogens by the host immune system that recognizes and eliminates them. However, the immune system has coevolved to live in a collaborative relationship with the healthy microbiota [45].

The GM colonizes human intestine and plays an important role in both health and disease. A healthy adult's intestine harbors with a rough estimate of about 38 trillion bacteria making it the most densely and diversely populated organ on the body [46]. In order to maintain immunological homeostasis, the gut microbiota plays an important role. The mucosal immune system, particularly mucosa-associated lymphoid tissue (GALT) and bronchialassociated lymphoid tissue (BALT), is critical because it serves as the first line of defense against pathogens [47].

The immune cells of the GALT and gut microbiota must communicate in order to modulate the immune system. The significance of gut microbial products in maintaining the balance between regulatory T cell and effector T cell response has been well investigated [48]. In addition, It regulates apoptosis, cellular differentiation, and chemical modification of nuclear proteins and nucleic acid, as well as maintaining the integrity of the intestinal epithelial barrier through the production of short-chain fatty acids, particularly butyrate, which are important in providing energy for cellular metabolism [49].

Signals from intestinal bacteria are known for priming systemic immune responses and for regulating pro- and anti-inflammatory host immune responses these include T regulatory cells (Tregs) and T helper 17 (Th17) cells. Commensal organisms like fragilis and Clostridial species aid Treg differentiation in the gut. In addition, segmented filamentous bacteria trigger the production of Th17 cytokines and the maturation of natural killer T cells [50-52]. Different genetic and environmental factors influence the GM composition among individual, but the human body will gradually establish a stable intestinal flora structure and regulate the body's health [53].

Thus, the immunological function of GM cannot be neglected. In SARS-CoV-2 infected patient's gram negative bacteria and inflammatory cascade was increased, however, anti inflammatory and beneficial bacteria was decreased. Further more ,various studies have showen that disruption of intestinal homeostasis and dysbiosis in the intestinal microbiome play a role in a variety of diseases, including respiratory infections, depression, type-2 diabetes, cardiovascular disease and hypertension [54-58].

Gut-Lung Axis

A close relationship exists between the gut and lung is named "gut-lung axis" because of anatomical, functional and bidirectional character. GM as a "virtual metabolic organ" makes axis with a number of extra intestinal organs, such as kidneys, brain, cardiovascular, and the bone system, but the gut-lung axis attracts increased attention in recent years [59]. The symbiotic relationship between the GM and the lung is regulated and stabilized by a complex network of interactions that encompass metabolic and immune crosstalk between them [60]. The gut-lung axis is reportedly bidirectional, that microbial components like endotoxins and metabolites from the gut can affect the lung through the bloodstream and in case of lung inflammation, the gut microbiota could be impacted as well [61].

The immunological axis connecting the lungs and the gut has a significant impact on microbial invasion resistance. In other words, the interaction between the gut microbiota and lung pathology via the gut–lung axis is crucial in determining disease severity. The Depletion of gut microbiota has been associated to alveolar macrophage dysfunction and a reduction in reactive oxygen species-mediated bacterial killing potential [62].

Furthermore, there is a link between antibiotic-induced disruption of the gut microbiota and improved Mycobacterium TB survival in the lungs in patients with a high risk of disseminated tuberculosis has also been reported [63]. In addition after being exposed to the influenza virus, CCR9+CD4+ T cells from the lungs travel to the intestine, where they modify the gut microbiota, resulting in an abnormal Th17 response with intestinal damage and gastro enteritis [64].

Gut microbiota in COVID-19 patients

Now, there is emerging evidence that global pandemic of COVID-19 disease has been associated with an imbalanced intestinal microbiota homeostasis, which has qualitative (dysbiosis) or quantitative (overgrowth) differences [33-35]. Recently, some researchers are beginning to investigate the relationship between the diversity and composition of human gut microbiota and SARS-CoV-2 infection. Severe acute respiratory syndrome coronavirus 2 infection exhibiting change in the relative levels of "beneficial" and potentially "harmful" bacteria compared to healthy subjects, however the dynamic dysbiosis of the gut microbiota following SARS-CoV-2 infection is still unknown [37, 65]

The structural changes in the intestinal microflora and the severity of disease are mutually causal. The gut microbiota in SARS-CoV-2 infected patients have a number of pathogens and opportunistic pathogens were enriched including *C. hathewayi, B.nordii, A.viscosus,* and a higher baseline abundance of C.hathewayi correlated

with more severe COVID-19 [33]. Additionally, these authors also discovered that the intestinal micro flora structure of the SARS-CoV-2 infected patients had changed compared to that before severe disease progression, which indicated that the alteration of intestinal flora played a potential pathogenic role in patients with SARS-CoV-2 (33). *Tao et al*. have demonstrated that change in the quantity and composition of fecal bacteria in COVID-19 patients compared to healthy control group. The pattern of the gut microbiota composition was found to be positively correlating with increased expression of IL-18, the pro inflammatory cytokine [59].

Recent research result showed that COVID-19 patients have been found to have lesser beneficial gut microbiota and to host more opportunistic pathogens. Interestingly, COVID-19 severity was shown to be favorably correlated with the presence of opportunistic pathogens and negatively correlated with the presence of the anti-inflammatory bacterium Facealibacterium prausnitizii [33]. In addition, the presence of a few bacteria such as Streptococcus and Bacteroides correlates negatively with inflammatory cytokines and positively with a few other groups of gut microbiota, suggesting that gut microbiota may play a role in COVID-19 patients' tendency to disease severity. Similarly, in COVID19 patients, perturbation of enteric RNA and DNA viral florahave been identified, and the severity of the disease has been linked to the changes in gut virome [66].

Surprisingly, a recent study that used a systems biology approach to examine the levels of 50 gut-associated plasma metabolites found that the majority of these metabolites were found to be dysregulated during severe COVID-19 as compared to controls and individuals with mild disease. Citrulline, an amino acid that is a well-established measure of gut and enterocyte function, was found to be considerably lower in the study. During severe COVID-19, levels of succinic acid, a well-known indication of gut microbial dysbiosis, were also shown to be rising [67]. In general, the expansion of intestinal pathogenic bacteria leads to increased mucosal permeability, which cause of systemic immune activation in SARS-COV-2 infection. Therefore, these accumulating studies suggest that dysbiosis in the composition of gut microbiota play a significant role in induction and furthering the severity of COVID-19 disease.

Immune Function of Gut Microbiota on severity of COVID-19

Different studies indicated that the composition of the gut microbiota affects the host immune response to SARS-CoV-2 infection , and it can easily aggravate the clinical course of disease when the intestinal flora is altered [59, 66]. The immune injuries caused by structural changes in the gut microbiota is mostly driven by inflammatory pathways, which are initiated by crosstalk between the gut microbiota, immune system, and lung [68, 69].

Different immune cells capable of expressing TLR that recognize pathogen associated molecular patterns (PAMPs) and initiating the innate immune response. It is now known that the intestinal PAMPs associated with SARS-CoV-2 infection are mainly composed of lip polysaccharide (LPS). The introduction of this endotoxin into the bloodstream causes the release of cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6), IL-10, and the soluble version of the IL-2 receptor, resulting in adult respiratory distress syndrome and multiple system organ failure [70]. In severe cases, this is accompanied by a decrease in the number of circulating lymphocytes (CD4, CD8, and innate lymphocyte populations), as well as a decrease in monocytes and dendritic cells, as well as their associated activation indicators [71]. As a result, the dysregulated recruitment and pro-inflammatory activation of monocyte-derived macrophages is thought to be mediated by a decrease in clearance of dead lung cells and subsequent diffusion of pro-inflammatory lipid mediators from these cells [72].

Native gel separation and micro scale thermophoresis assay data showed that the envelope glycoprotein of SARS-CoV-2 (Spike) can bind to E. coli lipopolysaccharide (LPS) and lipid A— the toxic part of LPS that is conserved among Gram-negative bacteria. Spike protein was found to bind to LPS with a similar affinity to CD14, the immune cell receptor that captures LPS and transfers it to toll-like receptors for inflammatory activation [71]. Another study done in animal models showed that, injecting LPS to simulate Gram-negative infection is enough to cause a cytokine storm [32]. This process involved Toll-like receptor 4 signaling, which was able to reverse the decreased bacterial killing activity of alveolar macrophages as well as elevated levels of IL-1, IL-6, and MIP-2 in the lungs as a result of commensal reduction [70].

Lipo polysaccharide (LPS) is a critical component of the outer membrane of Gram-negative bacteria and is an endotoxin mainly released by Enterobacteriaceae. Under physiological conditions, low concentrations of endotoxin entering the lung. However, during SARS-CoV-2 infected patient's pathogenic organism produce high amount of endotoxin. This Lipo polysaccharide binds to LPS-binding protein, and this combination can be identified by TLR4 on the surface of mononuclear macrophages [73].

Several studies have linked LPS to T cell activation and increased proinflammatory responses, resulting in a "cytokine storm" [74]. COVID-19 patients have higher levels of CXCL10 than healthy controls, according to studies. The CXCL 10 levels were higher in COVID-19 patients who needed to be admitted to critical care than in those who did not [75]. This study backs up the idea that LPS plays a role in COVID-19 severity. Studies also reported increased Levels of IL-1B, IFN-g, CXCL-10 and CCL2 have also been seen as a result of Th1 responses [76]. Infected and severe cases of infected patients had abnormal expressions of a battery of proinflammatory cytokines and chemokines, including IL-6, IFN-a, IFN-g, IL-1b, IL-12, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IP-10, MCP-1, MIP-1A, MIP1-B, PDGF, IL-18 [77, 78]. In severe and fatal lung damage instances, high LPS levels have been found [79].

This indicates that LPS may have a role in the pathophysiology of the COVID-19 cytokine storm and COVID-19-related microvascular problems, which needs to be explored further. In some COVID-19 cases, alteration of gut microbiota may allow LPS translocation into the portal circulation, which would further excite Kupffer cells in the periportal area of the liver, leading in NF-kB pathway activation and release of TNF-a and IFN-b [80]. This impact can cause hepatic as well as systemic inflammation, especially when LPS enters the circulatory system [81, 82]. Furthermore, the proinflammatory effect (IL-8, MCP1) of low dose LPS on endothelial cells, the high sensitivity of vascular smooth muscle cells to the stimulatory action of LPS, the link between endotoxemia and atherosclerosis, and the effect of LPS on insulin resistance are all significant factors that could serve as fertile soil for triggering the COVID-19 cytokine storm and microvascular injury in the COVID-19 cases [83-85].

The cytokine storm could be triggered by LPS-induced CXCL10 expression, as previously stated, or by the direct viral effect on the immune system. Generally dysbiosis in gut microbiota and colonization by opportunistic bacteria may boost the risk of developing comorbid conditions in patients with COVID-19 induced lung disease. Restructuring those gut microbiota is successful treatment for those patients.

Future Prospect of Fecal Microbiota Transplantation

The first step in developing a new therapy is to establish the goal, such as disease progression reversal or prevention, immune homeostasis improvement or maintenance, or death prevention. Since the beginning of the COVID-19 epidemic, several efforts have been made to discover a specific treatment for SARS-CoV-2, despite the lack of evidence for the efficacy of current SARS-CoV-2 medications [86]. Here, we will discuss a new prospective therapeutic for patients with severe SARS-CoV-2 infection. Studies on the gut microbiota have recently revealed a potential therapeutic target [43].

The gut microbiota may provide fruitful ground for disease prevention and treatment in humans. Numerous studies have shown that modifying the gut microbiota can be an effective technique for curing and maintaining diseases. Fecal microbiota transplantation (FMT) refers to the process of infusing faecal suspension from a healthy donor to a recipient's intestinal tract to normalize the composition and functionality of the intestinal microbiota. FMT repairs a damaged gut microbiota and may influence immune responses, especially in the respiratory system ('gut–lung axis'); such microbiome-immune signalling may result in lung-epithelial resistance to SARS-CoV-2 [87, 88].

Currently, FMT is one of the most promising treatments for SARS-CoV-2 infection. FMT was performed in 80-year-old man with many comorbidities, including past CDI, who was admitted to the hospital with pneumonia/sepsis, FMT was performed. Pneumonic symptoms improved after treatment with meropenem, but CDI relapsed. The patients were given sequential vancomycin therapy and nasojejunal FMT. He developed a fever and his C-reactive protein (CRP) level increased on the day after FMT; repeat microbiological cultures were negative, but SARS-CoV-2 PCR was positive. He began remdesivir and convalescent plasma therapy (CP). Unexpectedly, the fever never returned after FMT, and his CRP dropped, without further pneumonia exacerbation [89].

In another study, a 19-year-old immunosuppressed man with ulcerative colitis was admitted to the hospital due to a CDI relapse. After receiving vancomycin medication, the patient's symptoms improved, and colonoscopic FMT was performed to prevent recurrence. He developed a fever of up to 39°C fifteen hours after the FMT, with elevated CRP and interleukin-6 (IL-6) levels, and a positive SARS-CoV-2 PCR. His temperature did not exceed 36.6°C after that, with the exception of two isolated episodes of fever, and his CRP and IL-6 levels returned to normal [90].

Conclusion

The novel corona virus SARS-CoV-2 infection and the COVID-19 pandemic has turned into a global public health and economic disaster. Numerous studies have shown that COVID-19 has a distinct GM profile that is significantly linked to certain metabolic status and immunological responses.

Microbial translocation from the gut to the lungs can cause sepsis and acute respiratory distress syndrome due to inadequate intestinal integrity. Studies have shown a relationship between the gut and the respiratory system, as well as how the gut and respiratory tract work together to modulate immune responses and modify gut microbiota. Viruses that cause respiratory illnesses in the lungs have also been documented to spread throughout the body via the gut-lung axis. Therefore, the importance of gut microbiota should not be overlooked; rather, careful attention to patients' intestinal microbiota should provide a sound basis for COVID-19 treatment.

Since the beginning of the COVID-19 epidemic, many efforts have been made to discover a specific treatment for SARS-CoV-2, but the evidence on efficacy of current SARS-CoV-2 medications is insufficient. So, we have pushed forwards for the use of fecal microbiota transplantation. FMT strategies to remain safe and effective during and after the pandemic, Moreover, elucidating the role of gut microbiota and the gut–lung cross-talk in respiratory diseases can lead to novel microbiome-based preventative and therapeutic interventions for COVID-19 by manipulates the human commensal bacteria. However, the available data in this field remain limited and more research is urgently needed. An in depth understanding of the mechanism of action between gut microbiota and SARS-CoV-2 relates disease is required. It should be further studied for future.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Authors' Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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