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Abstract

A novel coronavirus (severe acute respiratory syndrome coronavirus [SARS-CoV-2]), has been causing a COVID-19 pandemic of acute respiratory syndrome in humans since December 2019. It appears to be similar in structure to the virus that caused the SARS-CoV outbreak of 18 years ago. However, in addition to the respiratory disorders, the COVID-19 patients might suffer extra-pulmonary disorders, including gut dysfunction or liver dysfunction complications, which show as gut–lung crosstalk. Fecal specimens should be considered as a source of detection of SARS-CoV-2 as one of the routine diagnostic tests in order to guide hospital's liberation and release of quarantine of patients.

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Introduction

The gastrointestinal and respiratory tracks both contain commensal bacteria. Identification of those bacteria can be very useful. The role of microbiota in a healthy immune response is generally well accepted, while gut dysbacteriosis might result in chronic inflammatory lung diseases, hence their identification could be indicative of other diseases. Intervention to change the gut microbiota may decrease disease severity. Thereby, detecting the role of microbiome in viral diseases, and developing the novel therapeutic strategies to change the microbiome by probiotics, personalized diet, and traditional Chinese medicine to regulate the immune system and restrain cytokine storm is pivotal.

Materials and Methods

Articles related to this topic were searched in PubMed, Scopus, Web of Science, Embase, Directory of Open Access Journals (DOAJ) and Google Scholar, using the following keywords or their combinations; COVID-19, SARS-CoV-2, ACE2 receptors, gastrointestinal microbiota and gut microbiota.

Angiotensin-converting enzyme 2 receptors

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) has been causing the COVID-19 pandemic of acute respiratory syndrome in humans since December 2019. It appears to be similar in structure to the virus that caused the SARS-CoV outbreak of 18 years ago (1,2).

One study used molecular modeling to show structural similarity between receptors of the SARS-CoV and COVID-19, therefore suggesting angiotensin-converting enzyme 2 (ACE2) as the receptor for COVID-19 (1, 3).

It is recognized that ACE2 is widely distributed in the epithelia of the lungs and small intestines, whereas lower expression has been observed in the crypt cells and the colon (2).

COVID-19, in addition to pulmonary involvement, can cause liver and gut dysfunction, suggestive of gut–lung crosstalk (1). ACE2 receptors in human enterocytes are digestion-related enzymes and act as a conserved cell reservoir for coronaviruses. Interestingly, dipeptidyl peptidase-4 (DPP4) and alanine aminopeptidase are highly expressed in enterocytes in the small intestines of mice and act as receptors for other coronaviruses of MERS-CoV and

Key point

Recent research highlights the existence of a "gut-lung" microbial axis and its impact on lung diseases. Gut dysbiosis has a negative impact in response to COVID-19 treatment, particularly in patients with progressive lung disease.

HCoV-229E respectively (3). Zhang et al analyzed lung, esophagus, gastric mucosa, ileum and colon data in order to identify prime target cells of SARS-CoV-2 by comprehensive dissection of ACE2 and trans-membrane protease serine 2 (TMPRSS2) co-expression pattern. Preventive health outcomes may be influenced by these findings (4).

Digestive system

The descriptive, multi-centric study, with 204 COVID-19 patients, showed half the patients were reported to have digestive symptoms such as anorexia, diarrhea, vomiting, abdominal pain and higher liver enzymes. In rare cases, there were patients with digestive and hepatic symptoms without respiratory symptoms. Various hypotheses have arisen to explain digestive and hepatic symptoms in COVID-19. First, SARS-CoV-2 binds to ACE-2 receptors throughout the whole human body, inclusive of the digestive and hepatic systems. Second, using an inflammatory response, SARS-CoV-2 causes direct and/or indirect damage to the digestive system. Third, SARS-CoV-2 causes impairment of the gastrointestinal microbiota in the human intestine (4).

There is evidence that SARS-CoV-2 infects mature human enterocytes through TMPRSS2 and TMPRSS4 serine proteases by inducing cleavage of the S protein and enhancing membrane fusion (5).

Recent evidence showed that 15–53% of the patients with COVID-19 suffer mild to moderate liver injury with elevated aminotransferases, hypoproteinemia, and prothrombin time prolongation, with a frequent mild rise in serum bilirubin. Although the mechanism of liver injury is not completely understood, the liver injury can be due to direct viral infection of hepatocytes, immune-related injury, or drug hepatotoxicity (6,7). Moreover, Chai et al showed the expression of ACE-2 receptors in cholangiocytes, which causes liver abnormalities in patients with COVID-19 (8).

Postmortem liver biopsy of individuals with COVID-19, exhibited microvesicular steatosis and mild lobular activity (9). The “gut-lung” microbial axis and its impact on lung disease development, has been explored in recent research. For example, it has been recently shown that histamine secretions from the gut microbial are higher in asthmatic patients versus healthy persons (10). It has been suggested that “early-life” microbial exposure might affect the immune response and subsequently cause lung diseases (11).

Whether the virus gets to the digestive tract via cellular divisions from the respiratory system or clones in the digestive system is not clear. It is still practically recommended to take primary steps to inhibit fecal–oral transmission in public and in the hospital. The existence of fecal-respiratory and fecal–oral transmission route in patients with COVID-19 has been confirmed. Therefore, a need for further clinical trials and using antiviral drugs directing digestive system is warranted (12).

Fecal transmission

Asymptomatic children and adults may be able to transmit the SARS-CoV-2 virus particles to others through fecal shedding. Fecal specimens should be considered as a source of detection of SARS-CoV-2 as one of the routine diagnostic tests (13).

The analysis of fecal microbiota is the most common way to investigate gut microbiota (14). A pilot study with 15 hospitalized patients with COVID-19 showed continuous changes in the fecal microbiome versus the control subjects, which were associated with the severity of COVID-19 too (15). More studies need to expose its reproduction ability, is transferability in stool and its stability in the environment that would interrupt SARS-CoV-2 as well to distribute it among human hosts.

Gut microbiota

Based on hygiene hypothesis, gut microbiota has been known as one of the main factors of increasing incidence of immunity-associated diseases. For example, metabolic syndrome, allergic disorders, liver disorders, cardiovascular diseases, neurodegenerative diseases, and cancer, could be targeted and treated more efficiently by better recognizing of gut microbiota in personalized healthcare (16). It is proposed that manipulation of the gut microbiota can prevent or decrease the intensification of lung diseases. The role of gut dysbiosis in lung diseases comprising allergy, asthma, chronic obstructive pulmonary disease, cystic fibrosis and lung cancer, have been observed by extensive studies (14,16,17).

Over the past years, studies with poliovirus, norovirus, mouse mammary tumor virus and influenza virus have shown the connections between the microbiota and virus infections (18). Numerous investigations have found that when the gut microbiota is harmonized, it can decrease inflammation of the small intestine and ventilator-associated pneumonia and in addition, it has been noted that this can also reduce side effects of antibiotics against influenza virus replication (19).

The microbiota may have direct or indirect effects on viral infection (17). Microbiota is able to change the host immune systems and regulate the responses to various viral pathogens (20).

The variety of intestinal microbiota and the existence of advantageous microorganisms in the intestinal tract could play a vital role in prevention, treatment and also the duration of COVID-19 disease (21). A potential target to fight against SARS-CoV-2 could be to decrease intestinal ACE2 expression by some specific gut microorganisms. In fighting COVID-19, enhancing the immune system by modulating the gut microbiome should be considered as a therapeutic option. One way for advancing a healthy microbiome may involve procedures to increase intestinal butyrate production and decrease pro-inflammatory

conditions via nutritional alterations (22).

It is interesting to study whether variations of gut and/or lung microbiota may modulate the reaction of ACE2 on enteric viruses. However, gut microbiota enhances antiviral immunity by increasing the number and function of immune cells, reducing immunopathology, and inducing interferon production (23). The effects of commensal bacteria to facilitate the viral attachment to the host enteric cells and ensue infection have been shown. Any intervention in microbiota-virus interactions may be considered as a new, therapeutic methods in preventing the disease (24).

A study by Herbst et al confirmed that airway inflammation and hypersensitivity induced by ovalbumin is much weaker in specific pathogen-free environment mice that were colonized with commensal microbes compared to germ-free mice (25,26). The recognition of commensal bacteria in both respiratory tracts and the gastro-enteric region might be an important and inventive subject. The role of microbiota in a healthy immune response is generally well accepted, while gut dysbacteriosis might result in chronic inflammatory lung diseases.

The dysbiosis gut activates inflammatory pathways and leads to bronchoconstriction and bronchial hyperresponsiveness. The phyla Bacteroidetes, Actinobacteria, and Firmicutes are prevalent in the healthy gut and lung microbial composition. The abundance of Proteobacteria with genera *Haemophilus* and *Moraxella* have been observed in persons with lung disorders (27).

The gut-lung crosstalk effects of gut microbiota are partly associated with producing metabolites, including short chain fatty acids, which could repress lung inflammation through the activation of serpentine receptors (28).

Melatonin and sodium butyrate are actively inhibited by most viruses. Benefits of melatonin and sodium butyrate in the management of COVID-19 emerge from induction of the melatonergic pathway and their ability to decrease the gut permeability (29). Stress also causes variations in gut microbiome, gut permeability, circadian rhythm and mitochondria, which look to be similar to the changes, induced by viruses; including a decrease in both melatonin and butyrate, thereby symbiosis in immune system and increase infection severity (30,31).

Some drugs, such as antibiotics and antiulcer medications, weaken gut and lung microbiota. The effective factors in intestinal dysbiosis are summarized in a review by Weiss et al. Natural variations induced by the changing supply of nutrients; drugs, the immune system, and the intestinal mucosa contribute to gut dysbiosis. The processes of stress factors, such as oxidative stress, the induction of bacteriophages, and secretion of bacteriocins changes microbial composition and cause reduced variety and growth of specific bacterial taxonomy (32).

Gut dysbiosis and COVID-19

In the hospital setting, gut dysbiosis may cause negative impact in response to COVID-19 treatment, particularly in patients with progressive lung disease. Therefore, the preventive or protective approaches of intestinal dysbiosis should be considered when combating with COVID-19 (32).

Zuo et al showed that persistent fecal microbiome alteration, is associated with fecal shedding of the virus and severity of COVID-19 (33).

Numerous small case reports from China showed reduced *Lactobacillus* and *Bifidobacterium* in some COVID-19 patients. Therefore, dietary modification with prebiotics and probiotics has been proposed (33).

A cohort study with 57 patients, investigated changes in the abundance of ten kinds of main gut bacterial groups in COVID-19 patients, using quantitative polymerase chain reaction (q-PCR), and explored the relationship of these groups with the severity of COVID-19 (general, severe, or critical). The results of this study showed that dysbiosis arisen in COVID-19 individuals since alterations in the gut microbial flora were related to disease intensity. Conversely, the abundance of butyrate-producing bacteria also significantly decreased the severity of the disease (34).

Nutrients and microbes

The gut in healthy humans includes more than 1000 bacterial species (35). According to previous discussions and improvement in our perception regarding the role of the microbiome in virus illness, the new therapeutic modalities to modify the microbiome through probiotics, personalized diet, and traditional Chinese medicine may help to regulate the immune system and restrain cytokine storm (36). A narrative review assesses scientific studies published from 2005 to 2019 and evaluated the effect of micro- and macro-nutrients including tea-derived polyphenols, dietary fibers, vitamins, supplementation of calcium, magnesium, phosphorus, selenium, zinc, quantity and type of fat and proteins on the constitution of the intestinal microbiome by in vitro and in vivo models, and the clinical trials by human studies. It was found that these nutrients have a beneficial effect on good flora and help to suppress harmful flora (37).

Plant/Western dietary patterns

Many investigators have reported relationships between numerous lifestyle parameters and lung diseases. Dietary patterns are associated with prevalence, incidence, pulmonary function, and exacerbation of lung diseases. The intake of raw vegetables is particularly important among healthy diets. However, a large amount of evidence supports the concept that plant-based diets and raw vegetable diets in particular, have beneficial effects on lung disease. It has been found that traditional dietary patterns were associated with higher proportions of Bacteroides (Bacteroidaceae) and Bifidobacterium (Bifidobacteriaceae, Actinobacteria) and a lower proportion of Prevotella (Prevotellaceae) relative to modified Western dietary

patterns (38). Fermentation of dietary fibers by the gut microbiota produced short chain fatty acids, such as butyrate, which inhibits pulmonary type 2 innate lymphoid cells functions and subsequent development of airway hyper-reactivity (37).

Probiotics

Probiotics are living organisms that are beneficial for health when consumed in adequate amounts; both in the form of diet and drugs. The antiviral activity of Plantiricin compounds, via binding with RNA dependent RNA polymerase, residual binding domain, and ACE2 has been illustrated (39).

The therapeutic potential of using pro- and prebiotics to prevent or reduce the risk of COVID-19 exacerbations is one important issue. Probiotics may modulate the gut microbiota to alter the gastrointestinal symptoms and may also protect the respiratory system. With China's guidance in early February, it was suggested that probiotics can be used to adjust gut micro- ecology and help to prevent secondary bacterial infections in patients with severe COVID-19 infections (1).

It is known that prebiotics such as wheat, bran, fructo-oligosaccharides (Fos), and galactosaccharides (Gos) increase butyrate levels, reduce inflammation and improve lung diseases (40). These probiotics may modulate the immune system. Experimental investigations have shown that introduction of probiotic bacteria such as Lactobacillus rhamnosus, Bifidobacterium lactis and Bifidobacterium breve, can reduce allergic response (41). Lung metagenomic studies on patients with COVID-19, revealed Prevotella proteins are involved in multiple interactions with NF-kB, which causing clinical severity of COVID-19 infection (42). A review of 11 randomized clinical trials containing a total of 2417 children who received probiotics showed the reduction of respiratory infection (43). One initial study suggested that prebiotic and probiotic use improved pulmonary function parameters and reduced the systemic production of Th2 cytokines in allergic asthmatics (44). Another study using a nutritional combination of a probiotic with fish oils and vegetable extracts which caused significant improvement in children with asthma and reduced the need for inhaled bronchodilators and corticosteroids, proposing that a combination of numerous methods may result in the best outcomes (45).

Possible mechanisms by which probiotic bacteria may exert antiviral activity are as follows: direct interaction to the virus as an adsorptive or trapping mechanism, stimulation of the immune system by interleukin, natural killer cells, Th1 immune response activity, IgA production and production of antiviral agents such as hydrogen peroxide, lactic acid, and bacteriocins (16,46). Two meta-analysis reported moderate efficacy of probiotics in reducing the prevalence and the course of respiratory tract infections with viral origin (47,48).

In an open-label, randomized-controlled multicenter trial, 235 severely ill adult patients on mechanical ventilation, were received probiotics (*Bacillus subtilis* and *Enterococcus faecalis*) versus placebo. The probiotics were shown to prevent significantly ventilator-associated pneumonia versus the control. The fundamental mechanism includes inhibition of the colonization of potentially pathogenic microorganisms in the gut by probiotics (49).

In China, 58%–71% of COVID-19 patients were delivered antibiotics, 2–36% of patients suffered diarrhea. However, there is conflicting evidence here, for example, while a 2012 meta-analysis (50) showed that probiotics reduced antibiotic associated diarrhea modestly. Additionally, a large randomized, placebo-controlled trial with 2941 patients (51) showed that combined probiotics of Lactobacilli and Bifidobacteria during 21-days did not decrease antibiotic-associated diarrhea.

Interventions to change the gut microbiota may decrease disease severity. The use of antibiotics may cause more damage to the healthy commensal microbiome and intensify gut dysbiosis in COVID-19 patients. It is suggested that avoiding of unnecessary antibiotic administration in the treatment of viral lung diseases can preserve the beneficial bacteria in the gut boundary (15).

It has also been reported that the expression of coronavirus receptors did not reduce when probiotics, such as segmented Filamentous bacteria, *Lactobacillus acidophilus* and *Bacillus clausii* were used (3). Therefore, the probiotic effect on gut microbiota and the pathogenesis of SARS-CoV-2 needs more research and irrational use of common probiotics for COVID-19 is not suggested (52).

In Europe, products other than probiotics are available as oral health products and have been tested in clinical practice. The use of a mouth rinses and/or nasal applications that contain cyclodextrins combined with Citrox could lower the SARS-CoV-2 viral load and reduce the nasopharyngeal microbiota, as they tend to coat the surface aerosol particles and droplets during coughing or sneezing. Clinical trials to assess the inhibitive effects of cyclodextrins - Citrox therapeutic oral biofilm rinses in the reduction of the viral load of the infection and disease progression is necessary (53).

Conclusion

Recent research highlights the existence of a "gut-lung" microbial axis and its impact on lung diseases. Gut dysbiosis has a negative impact in response to COVID-19 treatment, particularly in patients with progressive lung disease. The preventive or protective approaches of intestinal dysbiosis should be considered in combating COVID-19. Progressing our understanding about the function of the intestinal microbiome in viral illnesses, new therapeutic modalities, regarding the modifying of microbiome by probiotics, personalized diet, and traditional Chinese medicine to regulate the immune system and restrain

cytokine storm, can improve the outcome of COVID-19.

Authors' contribution

TS and MR prepared primary draft. AT edited the draft. Both authors read and signed the final paper.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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