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FMT: A Potential Therapeutic and Rehabilitative Intervention for COVID-19

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Abstract: Coronavirus disease 2019 (COVID-19), which was outbreak in December 2019 Wuhan, China, has spread to more than 100 countries. In addition to respiratory symptoms, COVID-19 can also cause some digestive symptoms such as nausea and diarrhea. As a variety of respiratory diseases which are associated with a dysbiosis in both airway microbiota and the intestinal microbiota, COVID-19 may cause digestive symptoms through a constant cross-talk between the system which is known as the Gut-Lung Axis. Additionally, lymphopenia and hypercytokinemia were also common in COVID-19 patients which suggest that COVID-19 could compromise the immune system. Given the fact that gut microbiota not only could maintain immune homeostasis and immune responses at local mucosal surfaces, but also has distal protective effects and protect against respiratory virus. FMT is an effective way to enhance immunity and would be a potential therapy for individuals with viral infection. However, currently no direct clinical evidence proved that modulation of gut microbiota has the therapeutic role in treatment of COVID-19, from the perspective of microbiota and immunity after viral infection, we speculate that targeting gut microbiota might be a new therapeutic option or at least adjuvant therapeutic choice. In this Personal View, we describe the five aspects: COVID-19 and compromised immunity system, Microbiota, immune system and viral infection, FMT, immunity and virus infection, potential application of FMT in the treatment of COVID-19.

Keywords: Coronavirus disease 2019; Potential Therapeutic; Rehabilitative Intervention

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1 Introduction

A number of unexplained cases of viral pneumonia occurred in December 2019 Wuhan, China. This initial cluster of patients with what soon became known as coronavirus disease 2019 (COVID-19) heralded the arrival of a new pandemic caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To date, more than 40 million cases have been confirmed in the world. The disease has spread to more than 100 countries, with new massive outbreaks reported in other countries including USA, Italy, Germany, Spain, et al. Both incidence and death are rising around the world. In this review, from the perspective of microbiota and immunity after viral infection, we describe fecal microbiota transplantation (FMT) as a potential therapeutic and rehabilitative intervention of

COVID-19.

2 COVID-19 and gastrointestinal symptom

Fever and cough are the most common clinical manifestations of COVID-19 infection. In addition, the disease often causes serious enteric symptoms, such as diarrhea and nausea, even more severe than SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV)[1,2]. According to the updated reports of COVID-19 clinical characteristics, 2-14.7% of COVID-19 patients exhibited diarrhea and1-5% of the case had symptoms of nausea and vomiting[3-7]. Among these reports, which includes a retrospective study of 1, 099 laboratory-confirmed cases with COVID-19[8], and another report describing a familial cluster, 2 of the 6 family members (33%) developed diarrhea[9].

There is mounting evidence that COVID-19 may be transmitted through digestive tract. Angiotensin-converting enzyme 2 (ACE2) is known to be abundantin the epithelia of humanlung and intestine. ACE2 can regulate intestinal amino acid homeostasis and the expression of antimicrobial peptides, thus is related to the gut microbiome ecology. ACE2 mutant mice exhibited altered intestinal microbial composition[10].In addition, it has been reported that expression of ACE2 in colonic epithelial cells is related to viral infection, innate and cellular immunity[11].

Actually, it has long been recognizedthat there were potential anatomic communications between the digestive and respiratory system by complex pathways involving their respective microbiota, which was supported by the fact that a variety of respiratory diseases have been associated with a dysbiosis in the intestinal microbiota. The constant cross-talk between the gut and lungs is known as the Gut–Lung Axis[12]. Therefore, it is very likely that COVID-19 could also cause digestive symptoms through the Gut-Lung Axis.

3 COVID-19 and compromised immunity system

One of the most common clincial characteristics of COVID-19 is lymphopenia which suggested a compromised immunity. Data regarding 1, 099 patients with laboratory-confirmed Covid-19 reported that 33.7% patients, especially 61.1% severe patients were have lower blood leukocyte count, and up to 82.1% patients, especially 95.5% of severe patients have decreased lymphocyte count[8].The recent articles in The Lancet revealed that 85% of the critical patients with COVID-19 showed lymphopenia[5,13]. Wang D et al. confirmed that lymphopenia was a characteristic of severe COVID-19, which was reported in a study published in JAMA. It reported that the median lymphocyte count of ICU patients with COVID-19 was 800 cells/mm^3, while the non survivors showed persistent lymphopenia[4].

Meanwhile plasma cytokines are also high in ICU patients[5]. The presence of both lymphopenia and hyper-cytokinemia in COVID-19 patients might indicate poor control of the pathogen, as previously demonstrated by severe patients of the influenza virus during the 2009 pandemic. Of interest, hypercytokinemia and lymphopenia were also apparent in critical patients infected by the coronavirus emerged in 2003 (SARS-CoV)[14,15].In addition to the coronavirus infection, hypercytokinemia and lymphopeniawere also observed in community acquired pneumonia. Increased disease severity and mortality, dysregulated immunological response was observed in patients with hypercytokinemia and lymphopenia. The observed lymphopenia in severe patient of COVID-19 may be partly explained by the direct cytotoxicity of the virus to lymphocyte. However, lymphopenia could also be attributed to host conditions. Compared with those patients with moderate symptoms, critical COVID-19 patients in the ICU are tend to be old and with other diseases conditions such as hypertension, diabetes, cardiovascular and cerebrovascular disease[4].

Therefore, similar to SARS and other respiratory virus, COVID-19can greatly compromise the immune system and lead to hypercytokinemia and lymphopenia, which can exacerbate the immune problems in the elderly patient group and those with complications.

4 Microbiota, immune system and viral infection

Themucosal surfaces of the human body such as intestine and respiratory tract is colonized by tens of trillions of microorganisms which are usually referred to as microbiota. These commensal bacteria are critical to human health due to their direct protection against exogenous pathogens and contribution to the

immune system. In the past decades, large amount of evidence emerged to support the beneficial effects of commensal bacteria, especially probiotics.

In addition to their crucial role in maintaining immune homeostasis of the intestine, studies also reported that commensal bacteria exerted a marked influence on the immune responses at other mucosal surfaces such as the respiratory tract[16]. Mucous membranes are important natural defence against pathogens including viruses. The crucial role of intestinal microorganisms in immune functionality was highlighted in a germ-freemice model in which microorganisms facilitated the development of a mature lymphoid structures within the gastrointestinal tract to establish the first line of defense of the intestinal mucosa[17].Rotavirus (RV) infected mice was treated with bacterial flagellin and innate immunity was activated through flagellin receptors TLR5 on dendritic cells, which elicited the production of IL-22 and induced the expression of a protective gene in intestinal epithelial to promote normal epithelium proliferation. Bacterial flagellin also stimulate the release of IL-18 which induces apoptosis of infected epithelial[18].Daily supplement of probiotic bifidobacteriumbreve mixed with galactooligosaccharides and fructooligosaccharides has a positive influence against rotavirus infective process and activates the early immune response for a future immune response against reinfection[19].

Intestinal microbiota could also activate the inflammasome and have indirect protective effect on virus influenza infection. The induced inflammasome activation can lead to migration of dendritic cells from the lung to local lymph node to stimulate prime influenza-specific T-cell response in the lung[20]. The intestinal microbiota regulates immunity in the respiratory mucosa by upregulating the TLR7 signaling pathway for the proper activation of inflammasomes and activing Th1 cells, CTLs to protect against respiratory influenza[16,21].There was alsoevidence that lactobacillus plantarum exhibited antiviral effects on influenza virus infection by modulating innate immune cell such as dendritic and macrophage cell, and cytokine production pattern[22]. Probiotics lactobacillus modulated lung immunity by reducing accumulation of inflammatory cell in the lungs and promoting faster viral clearance , thus was associated with an improved control of influenza infection and alleviated the burden of respiratory tract infections[23].

How the intestinal bacteria are able to improve antiviral immunity in the respiratory tract may partly be explained by the vital cross-talk between the mucosal surface of our body which is usually referred to as the Gut-Lung axis. The intestinal and respiratory system are closely connected, and the gut microbial metabolites could activate and promote the migration of immune cells to distal tissues to mediate antiviral effects[12]. Overall, gut microbiota not only can maintain immune homeostasis and immune responses from local mucosal surfaces, but also has distal protective effects and protect against respiratory influenza virus.

5 FMT, immunity and virus infection

Bradley et al reported thatantibiotic treatment could reduce instestinal microbiota, thus change the interferon signature driven by commensal in lung epithelia and promote early influenza virus replication in the respiratory tract. The effects that can be reversed by fecal transplantation[24].

It was reported that changes in intestinal microbiome during chronic human immunodeficiency virus (HIV) infection were relevant to mucosal dysfunction, inflammation and disease progression[25-27]. Tiffany HM et al. conducted FMT experiments on rhesus monkeys infected with chronic SIV during antiretroviral therapy. After antibiotic treatment, greatest microbiota shift was observed, while the frequencies of Th17 and Th22 in peripheral blood increased and the activation of CD4 T cells in intestinal tract decreased after FMT. On the one hand, Th17 and Th22, important components of mucosal immunity, were significantly depleted in HIV and SIV infection. Thus, they supposed that Th17 and Th22 might be restored by alteration of the microbiome through FMT. On the other hand, T cell activation is associated with CD4 T cell loss and disease progression in HIV infection.Therefore, they hypothesized FMT might have a beneficial effect on intestinal T cell activation. Overall, the study concluded that FMT might potentially have favorable effects on theimmune dysfunctionassociated with chronic infection[28]. We speculate that FMT can enhance immunity and would be a potential therapy for individuals with viral infection.

6 Potential application of FMT in the treatment of COVID-19

Currently no direct clinical evidence has proved that the regulation of gut microbiota has a therapeutic effect in treatment of COVID-19, but we suppose that targeting the gut microbiota might be a new treatment choice or at least an option for adjuvant therapy.

At the beginning of February 2020, the guidance of China's National Health Commission (5th edition) recommended that probiotics could be used to maintain the intestinal microecological balance and prevent secondary bacterial infection when treating patients with severe COVID-19 infection. It showed that a growing awareness of the importance of gut microbiota in COVID-19 infection had been accepted by Chinese government and first-line medical staff.

And also a line of clinical programs for FMT in COVID-19 have been initiated in china. Such as the program of "Washed microbiota Transplantation for Patients with COVID-19 Infection" which is sponsored by The Second Hospital of Nanjing Medical University (https://clinicaltrials.gov/ct2/show/NCT04251767). The "Application of fecal microbiota transplantation (FMT) in the treatment of COVID-19" program which was sponsored by Jiangxi Shanxing Bio-technology Co.,Ltd.. More attention and researches should be devoted to these programs.

7 A pilot study of FMT in discharged COVID-19 patients

A pilot study of FMT in discharged COVID-19 patients was conducted in the medical center of Ganzhou city in Jiangxi province after COVID-19 outbreak in China. A total of 11 COVID-19 patients were recruited in April, 2020, about one month on average after they were discharged from the hospital. Gastrointestinal symptoms, gut dysbiosis were generally observed in those COVID-19 patients during post-infection recovery. All subjects received FMT for 4 consecutive days by oral capsule (GanzhouShanjian Bio-technology Co.,Ltd., Ganzhou, China) administrations with 10 capsules for each day to improve the after effect of COVID-19 infection.

Significant improvement in digestive symptoms and restore of gut microbiome was observed after FMT treatment. In addition, alteration in the immune system, which include 69 different types of lymphocytes was also observed. All these results suggested a favorable effect of FMT on COVID-19 patients.

8 Conclusion

FMT is a favorable therapy with the possibility to treat a variety of diseases. Further research should be focus on this point. To sum up, we speculate that FMT could modulate the gut microbiota to favorably alter the gastrointestinal symptom and may also exert respiratory protection.

Given the fact that the new coronavirus is with high infection index and a great proportion of asymptomatic infection. Plus the reported positive dectection of the virus even in cured and released patients which put a great uncertainty over the pandemic of the virus. FMT can improve the immune functionality, restore the gut microbiota, alleviate gastrointestinal disorders. FMT might be as a potential therapeutic and rehabilitative intervention for COVID-19.

9 Contributors

Fengqiong Liu led the writing of the manuscript. Shanliang Ye and Jingsu Wang participate in modifying and reviewing the manuscript. Xin Zhu helps for the writing of the manuscript. Yuan fei Liu, Yong Li and Zhaoqun Deng developed the initial concept and framework for the manuscript and modified the drafting of the manuscript. All authors contributed to the content, drafting, and review of the manuscript.

10 Declaration of interests

The authors have declared that no competing interest exists.

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