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Interaction between gut microbiota and COVID-19 and its vaccine

Leung JSM. Gut microbiota and COVID-19 vaccines

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Abstract

The whole world has been continuously afflicted by the COVID-19 pandemic for the past three years. Many countries have tried many methods to control this virus infection with varying successes and failures. The gut microbiota is a biosystem spanning the entire length of the digestive tract and playing important roles in health and disease^[1]. It is much affected in the COVID-19 infection. In return it also substantially impacts on the infection. In particular, the gut microbiota has established a bi-directional interaction with the COVID-19 vaccines, enhancing or reducing vaccine efficacy by virtue of its varying components. Conversely, COVID-19 vaccines also make substantial impact on the gut microbiota, reducing its overall population and biodiversity. It is hoped that by exploring and harnessing this bi-directional interaction we may break new grounds and work out new methods to help preventing and treating this formidable virus infection.

Key Words: Gut microbiota; COVID-19 vaccines; vaccine interactions; gut microbiota alterations

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Core Tip: There is an urgent need to bring the ongoing COVID-19 pandemic under control, and one of the most important measures is vaccination. However, vaccines vary considerably in their efficacy and even for the same vaccine among the same population there is considerable variation in vaccine efficacy and side effects between individual cases. One of the more tangible and modifiable factors is the bidirectional interaction between the vaccine and the gut microbiota. This is a brief review of early studies and results showing how certain gut microbes could enhance the efficacy of a COVID-19 vaccine, while others would reduce such efficacy. There seems to be some gut microbes that might mitigate or exacerbate the side effects of vaccines. On the other hand,

vaccines seem capable of far-reaching effect on the gut microbiota, temporarily reducing their number and diversity. Further understanding and harnessing such interactions would have great potential in medicine and health.

INTRODUCTION

The gut microbiota is a highly important and intriguing biosystem extending throughout the alimentary tract, covering an area of 400 square meters and with a biodiversity spanning over 2,000 species, including protozoa, fungi, bacteria and virus^[1]. These organisms could be intraluminal or attached to the linings of the gut, some would even occupy an intracellular or subepithelial intercellular residence while still others might enter the tissue fluid, the lymphatics and even the blood stream^[1].

With such a background, the gut microbiota is constantly engaged in interactions with the various systems of the host and plays an important part both in health and in disease. In health, it is an integral part of digestion, absorption and nutrition. The contribution of gut microbiota in the production of vitamins of the B family and Vitamin K has become common knowledge. More recently, it has been shown^[2] that gut microbiota, with their rich endowment of enzymes, could digest far more varieties of carbohydrates than their host could do alone. Gut microbiota could also synthesize essential amino acids from inorganic nitrogen so that the host could survive even on a protein-free diet. In fat metabolism, some bacteria are able to synthesize long chain fatty acid, contributing to host energy supply as well as obesity, while many others, typically the strict anaerobes, ferment carbohydrates into short chain fatty acid (SCFAs). SCFAs inhibit HDACs (histone deacetylase) and activates G-protein coupled receptors (GPCRs) with benefits in anti-oxidant, anti-inflammatory, anti-tumorigenic and anti-degenerative functions^[3]. Indeed, research has shown the potential of fecal SCFA content as a marker of intestinal health, being at a lower level in colonic cancer *vs* healthy controls^[4]. Further studies of serum free fatty acid profiles especially the short chain fatty acid profiles show distinct patterns for healthy colon, colonic adenomatous

polyps, colonic cancer and coeliac disease reflecting the differences of gut microbiota among these conditions^[5].

It is beyond the scope of this review to cover all aspects of the gut microbiota in health and disease, but rather to focus on the intriguing interaction between the gut microbiota and the COVID-19 infection. The COVID-19 pandemic has been continuously ravaging the whole world for the past two and a half years. Up to the 22nd August 2022, the World Health Organization's statistics showed the cumulative number of infected cases exceeded 211 million and was still increasing at 4.5 million per week, while the cumulative number of death had exceeded 4.4 million and was still increasing at around 68,000 per week^[6]. Various well-established methods of infection control had been tried, mostly with only partial success, and complete control remained elusive. Meanwhile, the phenomenon of "pandemic fatigue" sets in and people become less inclined to adhere to control measures instead of tightening infection control measures^[7]. In this review, it is proposed to focus on some aspects of gut microbiota that are relevant to the pandemic and explore its potential contribution to pandemic control.

Gut manifestation in COVID-19 and microbiota alterations

The earliest report of COVID-19 in Lancet on January 24, 2020 on the first 41 cases in Wuhan stated that diarrhea was the presenting symptom in only one case^[8]. Three months later, when a New York center reported its first 393 cases of COVID-19^[9], diarrhea was the presenting symptom in 23.7%. The incidence of diarrhea in the two districts remained almost unchanged over the next year with China at 3.8% diarrhea among 1141 cases^[10] and New York at 20.14% diarrhea among 278 cases^[11]. The difference is obvious and significant. Conceivably the diet in the Wuhan population is quite different from that in New York. It is probable that the gut microbiota in these two localities would also have considerable difference, offering a plausible explanation of

the increased diarrhea among the New York patients. In addition a Western diet, rich in processed meat but deficient in microbiota accessible carbohydrates (MAC), would have lower bio-diversity^[12] and less favorable to health. Unfortunately for the research investigator, most of these early studies did not report details of gut microbiota status and the opportunity to study the influence of gut microbiota on the early phase of the pandemic was lost.

Gut microbiota alterations and COVID-19 severity

By 2021, it became obvious that gut involvement and diarrhea are associated with greater severity of COVID-19^[13]. An investigation in Hong Kong further demonstrated that certain components of gut microbiota with immune-modulatory potential were depleted in severe and long-lasting COVID-19, notably *Faecalibacterium prausnitzii*, *Eubacterium rectale* and bifidobacterial species^[14]. The investigators proposed that depletion of these bacteria could be taken as biomarkers predictive of severe and prolonged COVID-19. It is tempting to suggest that further studies might even explore the therapeutic value of replenishing these organisms to mitigate the disease.

Gut microbiota and the immune system and immune therapy

The interaction between gut microbiota and the immune system goes far beyond the three groups of bacteria mentioned in the last section. In fact, beginning with the first colonization of the gut at birth or even before birth, the gut microbiota continuously evolve and influence the development of the host immune system, fostering reactivity against pathogenic invaders and tolerance towards harmless colonizers or beneficial symbionts^[15]. Such actions are mediated by both regulatory cytokines (like IL-10, IFN-beta) and T-regulatory cells. This not only promotes diversity and increase of beneficial microbes but actually help(s) to reduce host autoimmune disorders.

On the other hand, antibiotics have been shown to reduce gut microbiota in both quantity and diversity, with reduced efficacy of immune checkpoint inhibitors (ICI) in immunotherapy of cancer and fecal transplantation has been shown to successfully restored the immune therapeutic response in such patients^[16].

Gut microbiota's impact on COVID-19 vaccines – efficacy and side effects

With the foregoing background we now come to the important consideration of controlling the ongoing COVID-19 pandemic. It is common knowledge that pandemic control rests on five pathways, (1) isolation of patients at the infectious stage by quarantines and social distancing, (2) blocking the routes of infection by masking, air filtering/exchanging and sanitation, (3) building up resistance among the population with vaccination, (4) development of effective medicines to cure the infected patients and get rid of the carrier status, (5) letting the pandemic run its natural course, eliminating all susceptible components of the population and leaving those with inborn or naturally acquired immunity to survive.

The first four measures at present runs into many obstacles, including social, economic, political, even personal egocentric considerations and biased sentiments. What is left is the fifth choice, otherwise called “herd immunity”, a rather primitive, counter-intuitive and inhuman approach. Fortunately, amidst these dark looming clouds appears a silver lining. The gut microbiota might not only modify the COVID-19 disease, but actually improve the efficacy and reduce the side effects of its vaccines, winning more sceptics to accept this highly important preventive measure.

This seminal work, a combined effort of the two Universities in Hong Kong, was reported by Ng *et al* and published on Feb 9, 2022^[17]. It shows that for vaccine-recipients of the inactivated virus, CoronaVac, the relatively low induction of neutralizing antibodies could be increased with a higher level of *Bifidobacterium adolescentis* in the gut

microbiota, while *Bacteroides vulgaris*, *Bacteroides thetaiotaomicron* and *Ruminococcus gnavus* were enriched in low responders. Another vaccine, the viral Spike protein-encoded messenger RNA, BNT-162b, under the brand name Comirnaty, although capable of eliciting high antibody levels, could be further improved by the abundance of flagellate and fimbriate bacteria like *Roseburia faecis*. In addition, for both vaccines, enrichment of *Prevotella copri* and two *Megamonas* species led to fewer side effects, likely due to the anti-inflammatory influence of these organisms.

Interestingly, the role of *Bifidobacterium adolescentis* in CoronaVac seems very specific. So far, according to these research workers, any other species of the same *Bifidobacterium* genus tested by them would not work. As the species *B. adolescentis* is not present in commonly available health food or probiotic preparations, there seems no way to simply make an off-the-counter purchase of “health foods” to obtain such benefit. By contrast, BNT-162b’s requirements on *Roseburia faecis* seem less fastidious, and various bacteria with flagella and fimbriae might also impart benefit. Even *Bacteroides thetaiotaomicron*, known to be associated with low antibody production in CoronaVac, joins the company of antibody-enhancers for BNT-162b. This list may also include a minimal existence of *Bifidobacterium adolescentis* because the only BNT-162b recipient who failed to develop adequate antibody level was entirely devoid of *Bifidobacterium adolescentis*.

Impact of COVID-19 vaccines on gut microbiota – a bidirectional interaction

Ng *et al* not only showed the impact of gut microbiota on vaccine efficacy, they also showed the impact of vaccination on gut microbiota one month after delivering two doses^[17]. For CoronaVac only *Bacteroides caccae* was increased. For BNT162b2 both *B. caccae* and *Alistipes shahii* were increase. Common to both vaccines, a large number of species were diminished including *Adlercreutzia equolifaciens*, *Asaccharobacter celatus*, *Blautia obeum*, *Blautia wexlerae*, *Dorea formicigenerans*, *Dorea*

longicatena, Coprococcus comes, Streptococcus vestibularis, Collinsella aerofaciens and *Ruminococcus sobeum*^[17]. There seemed to be a substantial loss of biodiversity, but no further elaboration on the clinical and pathological significance was mentioned. With such substantial change in the gut microbiota one would expect some alterations in bowel habits after vaccination. On a theoretical basis, vaccine-induced loss of diversity would increase the opportunity of pathogens to thrive in the intestine. There would be less competition for nutrition and for the niche of bacteria habitat, with less antagonistic factors produced by healthy bacteria such as bacteriocin and short chain fatty acids to discourage the growth of pathogenic organisms^[18]. With the proliferation of pathogenic organisms, the chance of diarrhea would be increased. Minor changes in bowel habits, however, tend to be under-reported and severe diarrhea would tend to be so uncommon that it is often under-powered to establish a statistically significant conclusion. The following table is constructed from data published online by the Centers for Disease Control and Prevention (CDC, USA).

While there is no significant difference in mild diarrhea between recipients of vaccine and placebo, a signal of increased severe diarrhea among vaccine recipients seems to show up at the bottom row for both first and second injections, possibly reflecting the increase in severe diarrhea by 3.2 to 3.8 times as a result of diminished diversity of gut microbiota. This table has two limitations. First, the actual number of severe diarrhea cases are too small for statistically significant computation. Second, no information is given for the composition of the microbiota of these patients and it is not possible to relate the diarrhea to any particular organism or to the vaccine itself.

Bidirectional interaction between gut microbiota and immune activities beyond COVID-19

Therapeutic agents, including vaccines, may have therapeutic value well beyond their originally intended effects. One of the best-known examples is the anti-tuberculosis

BCG vaccine, whose role in protection against leprosy is well studied and documented^[20]. For over 40 years it has also played a role in the treatment of non-muscle-invasive bladder cancer^[21]. Indeed, many vaccines have been actively studied as a platform for anti-cancer treatment^[22]. In certain areas, like hepatocellular carcinoma and carcinoma of cervix, anti-viral vaccines have successfully prevented the cancer by preventing infection of the respective oncogenic virus. In other cancers the mRNA technology has played pivotal role in stimulating the patient's immune system to recognize and react against tumor-associated neo-antigens^[23]. For three decades scientists have been struggling to iron out technical obstacles and the overall reluctance of recruiting the body's immune cells to produce an antigen and provoke an immune reaction, which is like retracing the steps of autoimmune disorders. (The same sentiment still prevails among COVID-19 vaccine doubters today.) Consequently, the predominant form of cancer immunotherapy at present went over to immune checkpoint inhibition which involves abolishing cancer's major mechanism of evasion from host immunity *via* immune checkpoints. Even in this context, certain components of the gut microbiota, notably *Bifidobacterium longum* and *Akkermansia muciniphila* are found to be associated with good response to checkpoint inhibitors in melanoma and lung cancer respectively, while lowered diversity and population of the gut microbiota under antibiotic treatment would have the opposite effect^[24]. When the COVID-19 pandemic broke out, the mRNA-based vaccines, backed by years of research in previous anticancer immunotherapy, had a chance to be tested extensively and speedily with resounding success.

CONCLUSION

As mentioned earlier in the study of Ng *et al*, certain gut microbes could enhance vaccine efficacy in antibody stimulation while other microbes have the opposite effect^[17]. Conversely, COVID-19 vaccines could impact on the gut microbiota, enhancing the growth of some microbes but suppressing the growth of many others^[17]. This bi-directional interaction between gut microbiota and COVID-19 vaccine is highly

reminiscent of that between gut microbiota and anti-cancer immunotherapy. Conceivably, modifying the gut microbiota might enhance the vaccine induced therapeutic value for both infection and cancer. It will take much further study to understand and possibly harness such interactions and convert their potential therapeutic value into reality.

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