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Review Article

The Role of the Gut Microbiome in Defense against COVID-19

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Abstract

The new coronavirus infection COVID-19, caused by the SARS-CoV-2 virus, was initially described as a "severe acute respiratory syndrome" leading to the development of fatal pneumonia. Later it was shown that the tropism of SARS-CoV-2 to the gastrointestinal epithelial cells is 100 times higher than in the respiratory tract, especially in the ileum. It has been established that although SARS-CoV-2 RNA elements are detected in the feces of patients, the virus itself is not there, and a fecal-oral route of transmission is impossible. In the lumen of the colon, viruses interacts with the gut microbiota and loses its infectivity. Perhaps it penetrates into the bacteria in the form of bacteriophages. We suggest using the virus's tropism to intestinal cells to form immune defenses. The formation of immunity and immune memory occurs at the level of the ileum in Peyer's plaques. If you inject a vaccine (RNA or attenuated live SARS-CoV-2) through the mouth into the small intestine, you can induce the development of intestinal symptoms and the formation of long-term immunity.

Keywords: *New Coronavirus Infection COVID-19; SARS-Cov-2 Vaccine; Intestinal Microbiome; Immunity*

Introduction

The coronavirus disease COVID-19 caused by the SARS-CoV-2 virus, which began in China back in December 2019, quickly spread to all countries on all continents. As of September 1, 2021, there were already 217 million officially registered infected people in the world and more than 4.5 million deaths from this infection. The actual data on sick and dead people can be significantly higher.

At the beginning of the outbreak of this infection, it was described as "severe acute respiratory syndrome", characterized by symptoms such as fever, cough, muscle pain, shortness of breath, pneumonia [1]. Later, other clinical signs of this disease began to be noted - conjunctivitis, skin rashes, anorexia, nausea and vomiting, diarrhea [2]. In a study conducted in the United States, symptoms of the gastrointestinal tract were observed in 61% of patients [3].

The transmission of the virus from a sick person to a healthy person occurred through close contacts, mainly through respiratory drops and through direct contact, including with asymptomatic carriers [4,5]. At the same time, SARS-CoV-2 RNA was detected in the feces of 48% of patients, in 70% of them fecal PCR remained positive after the disappearance of RNA from the respiratory tract [6,7]. It has been suggested that COVID-19 can also be transmitted by the fecal-oral route, causing a viral infection of the gastrointestinal tract [8].

Gastrointestinal form of COVID-19

For the first time, a gastrointestinal manifestation in COVID-19 was reported by Chinese transplantologists Gu., *et al*. in February 2020 [9]. It has now been established that patients infected with SARS-CoV-2 may not have any signs of visualization of pneumonia, but only symptoms from the gastrointestinal tract (GI symptoms). There were no significant differences in clinical outcomes (hospital stay, discharge, or death) between patients with and without gastrointestinal symptoms. The presence of SARS-CoV-2 RNA in feces does not always indicate gastrointestinal symptoms. However, SARS-CoV-2 RNA can be found in the esophagus, stomach, small and large intestine [10].

It has been reported that the angiotensin II-converting enzyme (ACE II) receptor is the main host cell receptor for the novel SARS-CoV-2 coronavirus and plays a crucial role in the binding and penetration of the virus into cells [11]. These receptors were identified in alveolar cells of type II lungs, in epithelial cells of the esophagus, enterocytes in the ileum and colon colonocytes, cholangiocytes, as well as in myocardial cells, proximal cells of renal tubules and epithelial cells of the urinary bladder [12,13]. Recently, it was shown that ACE II receptors are also expressed in the oral mucosa and epithelial cells of the tongue [14]. Thus, the oral cavity and the digestive tract may be the routes of entry for this infection, and the expression of the ACE II receptor in the gastrointestinal tract may explain the presence of gastrointestinal symptoms in patients with COVID-19 [15].

Recently, it was shown that the tropism of SARS-CoV-2 to epithelial cells of the gastrointestinal tract is 100 times higher than in the respiratory tract, especially in the ileum [16].

Viral nucleic acids were detected not only in samples from the nasopharynx, but also in saliva and feces [9,17]. For example, Zhang., *et al*. reported that detection of SARS-CoV-2 RNA in fecal samples was as accurate as in a pharyngeal swab, but patients with a positive stool test did not experience gastrointestinal symptoms [18]. In a Singaporean observation, the virus was detected in the feces of 4 out of 8 examined patients, regardless of the presence or absence of diarrhea [16]. In another study, the presence of SARS-CoV-2 RNA in stool was not associated with the presence or severity of gastrointestinal symptoms [10]. In addition, a positive stool RNA analysis was not associated with the extent of lung involvement [18]. More importantly, a group from China found that RNA was still present in the stool of more than 20% of SARS-CoV-2 infected patients who had negative conversion of viral RNA in the respiratory tract [19].

A number of authors show that SARS-CoV-2 RNA, determined by the PCR test in the feces of patients, is detected before 6 - 8 weeks of COVID-19 disease, when the disappearance of the virus in the nasopharynx, respiratory tract and bronchi and a decrease in Ig M in the blood serum is noted [20,21]. At the same time, it is not possible to isolate the infectious virus from the feces, apparently, its amount there is not large enough. Not a single case of "fecal-oral transmission" has been confirmed to date [21,22].

Gut microbiota and SARS-CoV-2 virus

A reasonable question arises: if a live virus enters the human gastrointestinal tract, why are its infectious properties not preserved in feces? This appears to be because it is neutralized by the human gut microbiota. The human microbiota is a complex endoecological system, represented by many types of bacteria and viruses. The total number of bacteria is 10 times, and viruses - 100 times the number of cells in our body [23,24]. Microorganisms make up about 50% of the solids mass of feces [25].

When a pathogenic virus enters the lumen of the gastrointestinal tract, it causes inflammation (acute gastroenteritis, enterocolitis). An example would be enteroviruses, rotavirus, poliovirus. Subsequently, the SARS-CoV-2 viruses, which are absolute parasites, penetrate the microbes living in the human colon and integrate their genetic material (bacteriophages) with them. The result is microbial lethal lysis, or a temporary symbiotic relationship, when viral genetic sequences are integrated into the host genome [26,27].

This was confirmed by work with cultures of epithelial cells of the human gastrointestinal tract and simulated liquid media contained

in various parts of the gastrointestinal tract, carried out by American and Chinese colleagues.

In the work carried out by R. Zang, an employee of the Department of Molecular Microbiology at the University of Washington and his colleagues, on a model of human intestinal cells, it was shown that the SARS-CoV-2 virus penetrates into mature human enterocytes through the expression of two muco-specific serine proteases (TMPRSS2 and TMPRSS4) [28]. They also demonstrated that viruses in the intestinal lumen were quickly inactivated by simulated human intestinal fluid, and the infectious virus was not recovered from stool samples from patients with COVID-19 [28].

Compared to rotavirus, which is transmitted by the fecal-oral route, SARS-CoV-2 loses its infectivity in low pH gastric fluids 10 minutes after incubation. However, the SARS-CoV-2 virus persists in simulated human small intestine fluid, which contains biological surfactants such as sodium taurocholic acid and lecithin. In contrast, the SARS-CoV-2 virus has been inactivated by several components in simulated human colon fluids. Zang R., *et al.* conclude that the SARS-CoV-2 virus replicates in human enterocytes in the small intestine, but can then be rapidly inactivated in the colon lumen. There is no live virus in the feces, but there is its RNA [28].

Gut immune system

In our opinion, the fact that this virus enters the small intestine, multiplies there and then becomes inactivated has a deep physiological meaning. The human small intestine, namely the ileum, contains the most important elements of the human immune system - Peyer's patches. In the mucous membrane in the area of these plaques are the so-called "antigen-presenting cells", which transmit information about the antigen (this can be the virus itself, its RNA or vaccine) to T-lymphocytes "helpers", and those, in turn, on B-lymphocytes, which, turning into plasma cells, begin to produce antigen-specific antibodies (IgM and IgG). T-helpers themselves stimulate the formation of so-called "cytotoxic" lymphocytes with a direct antiviral effect, as well as interferons. This is how the system of the antiviral immune response of our body works (Figure 1).

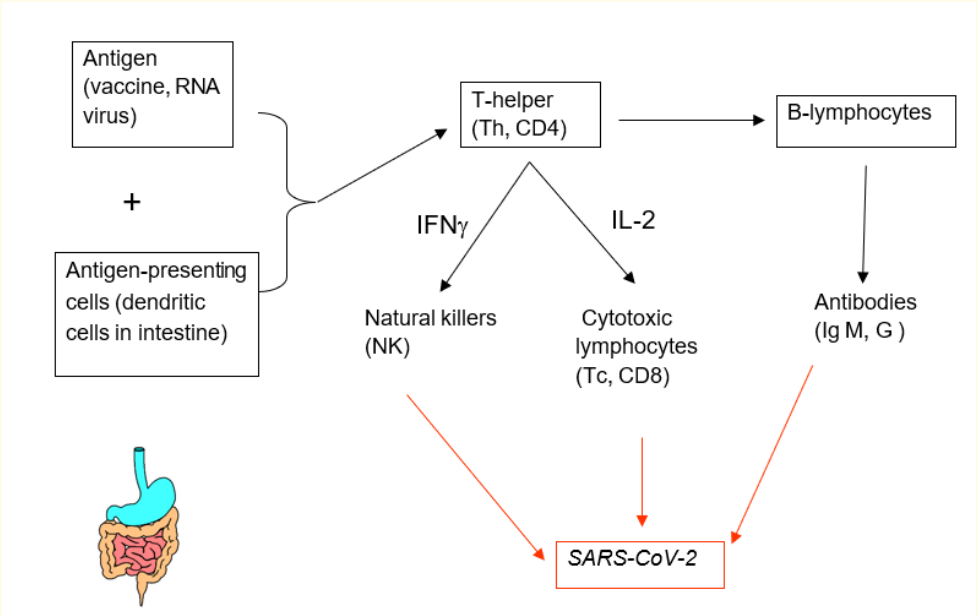

Figure 1: *Mechanisms of antiviral defense against SARS-CoV-2.*

In 1958, Russian scientists Anatoly Smorodintsev and Mikhail Chumakov developed a live oral intestinal vaccine against poliomyelitis (also an RNA virus transmitted by both airborne and oral routes). The vaccine was based on the live attenuated polio virus of Albert Sabin (USA). As a result of mass vaccination by 1961, 80% of the population (100 million people) were vaccinated, and the incidence of poliomyelitis decreased 120 times. This vaccine also stimulated the intestinal immune system and promoted type-specific, lifelong post-infectious immunity. In 2018, only 33 cases of polio were recorded in the world.

In connection with the above, we propose to introduce by the oral route (in the form of enteric capsules) into the lumen of the small (ileum) intestine:

1. Live attenuated viral vaccine SARS-CoV-2 (similar to the Smorodintsev-Chumakov poliovaccine).

2. RNA SARS-CoV-2, isolated, for example, from the feces of patients.

Problems of creating a vaccine against SARS-CoV-2

The SARS-CoV-2 virus undergoes mutations. Currently, about 200 of its strains are known. Around the world, vaccines against SARS-CoV-2 are being developed. However, most of them use the so-called "spike" ("spike" - or S-protein) for antigenic immune stimulation, which has the greatest mutagenicity and can cause an "antibody-dependent enhancement" (ADE), which consists of in the fact that antibodies that attach to viral particles lead to a more efficient infection of cells, and, as a consequence, to enhanced replication of the coronavirus and, thereby, to an increase in its pathogenicity [29]. This is what led to the fact that at one time an effective vaccine against the SARS-CoV coronavirus was not developed. This is why many scientists today express doubt that a safe and effective vaccine against SARS-CoV-2 will be developed anytime soon.

Evidence that antibodies produced against the S protein can harm by inducing ADE comes from the following observations. A comparative analysis of the specific humoral response showed that in patients who died from SARS-CoV, specific neutralizing antibodies to the S-protein were produced much faster than in recovered people. The ADE phenomenon is associated with a more severe course of the disease COVID-19 in the elderly. In this case, generalized infection and cytokine storm can develop [30,31]. This is supported by the fact that the amount of IgG antibodies to the S-protein of the SARS-CoV-2 virus detected in the serum of 29 hospitalized and tested patients linearly correlated with the age of patients, and the higher the titer of such antibodies, the more severe the disease progressed [32,33].

The ADE phenomenon, mediated by antibodies to the full-length S-protein of the SARS-CoV virus, has been observed in great apes. Despite the fact that vaccination reduced the viral load after infection with SARS-CoV, the presence of IgG antibodies to the S-protein in immunized macaques significantly increased inflammatory lung damage in real infection [34].

In many laboratories studying animal models of infections caused by severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) viruses, significant lung damage associated with ADE has been observed [35].

Upon repeated infection with SARS-CoV and MERS-CoV, the vaccinated animals fell ill again, and the lung damage was more severe than during the primary infection, despite the high level of specific neutralizing antibodies in the blood [36,37].

Specific antiviral immunity is associated with the production of interferons and immunoglobulins (antibodies) by blood lymphocytes. It has been shown that if interferons and antibodies are produced early, then they adequately neutralize coronaviruses. If their production is delayed, an inadequate immune response (shock, "cytokine storm") with damage to the alveoli of the lungs, kidneys and other internal organs can be observed [38,39].

Localization of SARS-CoV-2 infection in the epithelium of the bronchi and alveoli of the lungs is also a problem. Specific neutralizing antibodies that appear in the body as a result of vaccination should strengthen this barrier and prevent the virus from entering the lungs,

neutralizing it in the upper respiratory tract. Moreover, the presence of such antibodies in the blood, even with a high titer, may be insufficient to inactivate the virus precisely in the bronchial epithelium [40].

Conclusion

Thus, the new coronavirus infection COVID-19 caused by the SARS-Co-V-2 virus was initially described as "severe acute respiratory syndrome" leading to the development of fatal pneumonia. Later, it was shown that the tropism of SARS-CoV-2 to epithelial cells of the gastrointestinal tract is 100 times higher than in the respiratory tract, especially in the ileum. It has been established that although the elements of SARS-CoV-2 RNA are detected in the feces of patients, the virus itself is not there, and the fecal-oral route of transmission is impossible. In the lumen of the colon, the virus interacts with the microbiota and loses its infectivity. It is possible that it enters bacteria in the form of bacteriophages. We propose to use the tropism of the virus to intestinal cells for the formation of immune defense. The formation of immunity and immune memory occurs at the level of the ileum in Peyer's patches. If the vaccine (RNA or attenuated live SARS-CoV-2) is administered by mouth into the small intestine, intestinal symptoms and long-term immunity can be induced.

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