Review / Derleme

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Potential Neuroinvasion Mechanism of SARS-CoV-2

SARS-CoV-2'nin Olası Nöroinvazyon Mekanizmaları

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Abstract

The severe acute respiratory syndrome coronavirus-2, a coronavirus, is known to cause acute respiratory distress syndrome and a range of non-respiratory effects, particularly in elderly male patients with underlying health conditions such overweight, diabetes, and hypertension. The coronavirus disease-2019 sequelae include multiple organ failure and neurological issues, and these prior health issues are linked to endothelial dysfunction. Although inhalation is the most frequent mode of infection, this virus has also been discovered in neurons, cerebrospinal fluid, the choroid plexus, and meningeal vasculature.

Keywords: SARS-CoV-2, antiviral immunity, neurology, neuroinvasion, COVID-19

Öz

Bir koronavirüs olan şiddetli akut solunum yolu sendromu koronavirüsü-2'nin, özellikle obezite, diyabet ve hipertansiyon gibi sağlık sorunları olan yaşlı erkek hastalarda akut solunum sıkıntısı sendromuna ve bir dizi solunum dışı sekellere neden olduğu bilinmektedir. Bu sağlık sorunları endotel disfonksiyonla bağlantılıdır ve koronavirüs hastalığı-2019 sekelleri, çoklu organ yetmezliği ve nörolojik sorunları içerir. Solunum birincil enfeksiyon modu olsa da, bu virüs koroid pleksus ve meningeal arterlerin yanı sıra nöronlar ve beyin omurilik sıvısı dahil olmak üzere çeşitli organlarda keşfedilmiştir.

Anahtar Kelimeler: SARS-CoV-2, antiviral immünite, nöroloji, nöroinvazyon, COVID-19

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an infectious disease with an enveloped, single-stranded RNA genome that causes severe acute respiratory syndrome (1). SARS-CoV-2 spread to more than 200 nations and sparked a global epidemic. The members of the beta-coronaviriade family, SARS-CoV and Middle East respiratory syndrome (MERS-CoV), generally lead to upper respiratory tract infections while SARS-CoV-2 also causes lower respiratory tract infections (2-4). If we characterize the symptoms of SARS-CoV-2 from mild to severe, it can be characterized as fever, chills, difficulty breathing, nausea and/or vomiting. Serious symptoms include acute respiratory distress syndrome, pneumonia, sepsis, and bacterial infections accompanied by viral infections (5). The spike protein has to be cleaved by TMPRSS-2 and attach to the angiotensin-converting enzyme-2 (ACE-2) receptor in order for SARS-CoV-2 to invade cells (6). Type-2 pneumocytes in human lungs

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express high levels of ACE-2. The spike protein cut by these proteases is divided into 2 parts as S1 and S2. Of these parts, the S1 part interacts with ACE-2, and the S2 part infects cells by providing cell membrane fusion (7). ACE-2 receptor expression in the human body is not limited to the lung, but ACE-2 is also found in myocardial cells, renal proximal tubule cells, ileal and esophageal epithelial cells, and biliary urothelial cells. The presence of these receptors also makes these cells a potential target (8). In addition, studies showing Neuropilin-1 protein as a potential receptor for SARS-CoV-2 are available in the literature (9). As a result of the case studies in the literature, it has been shown that neurological symptoms and neurological diseases occur in COVID infection and post-infection status (10-14). According to case studies, the neurological findings of SARS-CoV-2 included dizziness, acute cerebrovascular illness, headache, reduced awareness, and ataxia (11-14). The neurological conditions linked to COVID-19 were categorized into five groups: encephalopathies, inflammatory central nervous system (CNS) conditions, ischemic strokes, peripheral neurological issues, and a number of other CNS diseases (11). In this review article, we wanted to address the immunological reaction and potential neuroinvasion mechanisms against other viruses and SARS-CoV-2.

Innate and Adaptive Immune Reaction Against SARS-CoV-2

Innate Immune Reaction Against SARS-CoV-2

When viruses infect a cell, they stimulate the immune response with pattern recognition receptors (15). Viral pathogenic motifs are sensed by pattern recognition receptors. The recognition of viruses by the immune system varies according to their genomic structure. According to the genomic structure of viruses, they have different receptors for DNA and RNA (16-18). Some of these receptors can recognize both RNA and DNA (19). Toll like receptor (TLR)-7 and TLR-8, located on endosomes, which are one of the entry routes of RNA viruses (ssRNA and dsRNA) into the cell, recognize viruses with genomes in the ssRNA and dsRNA structure (20). Viral RNA is recognized by cytosolic RNA receptors and activates RIG-1, MDA-5, LGP-2 and cGAS/STING pathway (21,22). By this recognition of RNA viruses, various pathways are stimulated and transcription factors are activated. These transcription factors are NF-κB, AP-1, IRF-3 and IRF-7. NF-κB and AP-1 transcription factors pass into the nucleus and provide transcription of chemokines (CCL2 and CXCL8) and cytokines [tumor necrosis factor (TNF) and interleukin (IL)-1] to activate and amplify the adaptive part of the immune system. IRF-3 and IRF-7 transcription factors pass into the nucleus and provide transcription of type-1 interferons, which are very important for the antiviral immune response (23,24). Type-1 interferons inhibit viral replication in the antiviral immune response, prevent the spread of the virus at an early stage and interrupt the communication of the cell with other cells at a later stage. Patients may have problems such as weariness, weakness, and coughing as a result of this process (25). Existing studies showing the suppression of type-1 interferon response during SARS-CoV-2 infection are available in the literature (Figure 1) (26).

Humoral Immune Reaction Against SARS-CoV-2

In viral infections, the humoral immune response is provided by the formation of neutralizing antibodies that can neutralize viruses, as in other infections. Some of the neutralizing antibody-producing B cells transform into memory cells and provide long-term protection by reducing the risk of reinfection in patients as a result of viral eradication (27). On average, on the fourth day of the illness in SARS-CoV-2 infection, an immune reaction is produced against N (nucleocapsid), one of the structural proteins of the virus (28,29). Immunofluorescence and ELISA-based screenings showed that specific antibodies against SARS-CoV in the immunoglobulin G (IgG) structure were present for 2 years. Immunoglobulin M (IgM) produced from B cells and plasmablasts acutely in the infection reached its peak level on the 9th day and the class change from IgM to IgG type was observed in the second week of the disease (27,29,30). It was still detected 6 years after SARS-CoV infection, but such long-term data for SARS-CoV-2 are not yet available in the literature (31).

T-Cell Immune Reaction Against SARS-CoV-2

The T cell-based antiviral immune response is based on the killing of the infected cell as a result of MHC-I dependent presentation of epitopes of the pathogen. With MHC- I, intracellular pathogens are cleared and T cells are enabled to recognize the pathogen (32). As a result of the eradication of the infective agent, T cells also transform into memory T cells and provide a faster adaptive immune response against the infective agent for a certain period of time. In SARS-CoV-2 infection, $CD8^+$ T cells have been shown to be stronger than the response to $CD4^+$ T cells in a study on 128 patients (20,33). IFN-γ, TNF-α, IL-2 and IL-12 released from T-helper 1 cells enable the activation of cytotoxic $CD8^+$ T cells (34-36). It has been demonstrated that the B cell response to SARS-CoV-2 is weaker than the T cell reaction to the nucleocapsid protein (37). It has been proven that peripheral blood mononuclear cells from patients still show an immune response to the nucleocapsid protein even after 10 years (Figure 2) (31,38-40).

Potential Neuroinvasion Mechanism of SARS-CoV-2

The central and/or peripheral neurological systems can be infected by viruses in a number of ways. The brain tissue is protected by the blood-brain barrier and increases the selectivity of the material to be taken into the brain tissue (41). SARS-CoV-2 primarily infects type-2 pneumocytes in the lungs in humans, but since viral spread is in droplets, it can be transmitted from any mucosal surface or open wounds (42).

Peripheral Route

It is possible to cause central nervous system infections or inflammation in the tissues of the central nervous system by being carried retrograde by neurons of Nervous Olfactorius with fila olfactoria in cavitas nasalis located in the cribriform palate, which is the first of the 12 cranial nerves found in the human nose. In a study conducted by Garg (43) on 114 patients with COVID-19, it was determined that there was a 54% loss of smell (44). The reason for the loss of taste in COVID-19 patients is

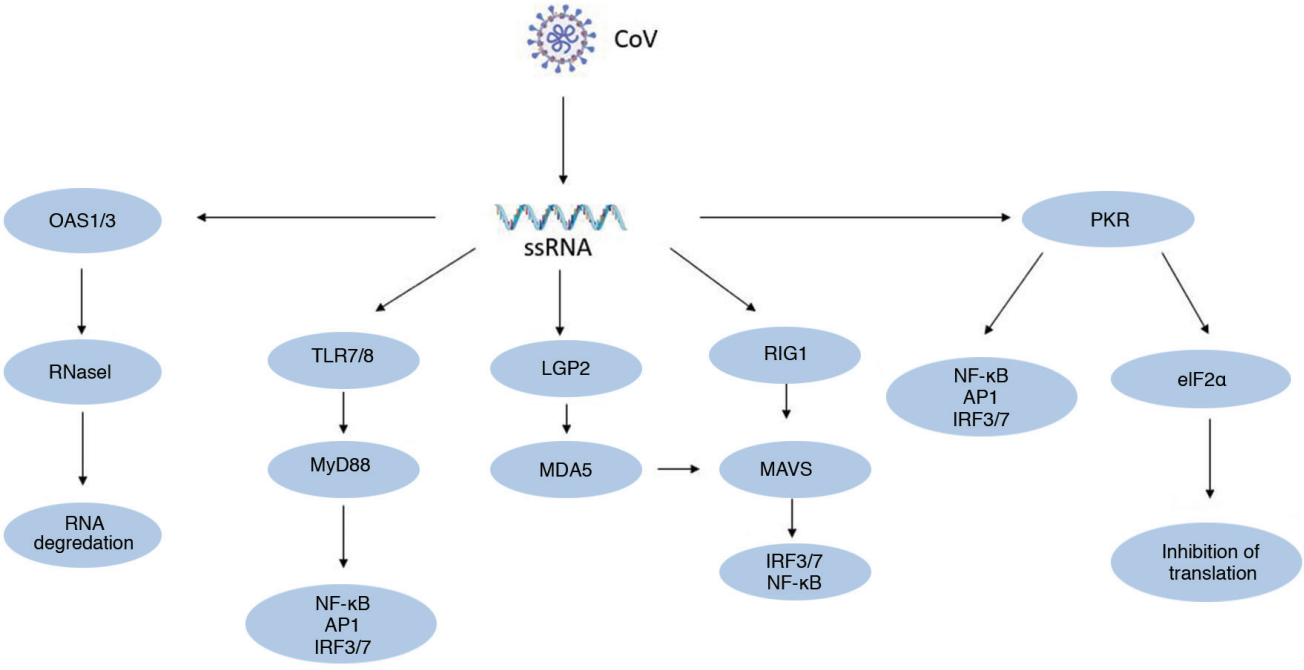

Figure 1. The sensing of viral ssRNA by pattern recognizing receptors.

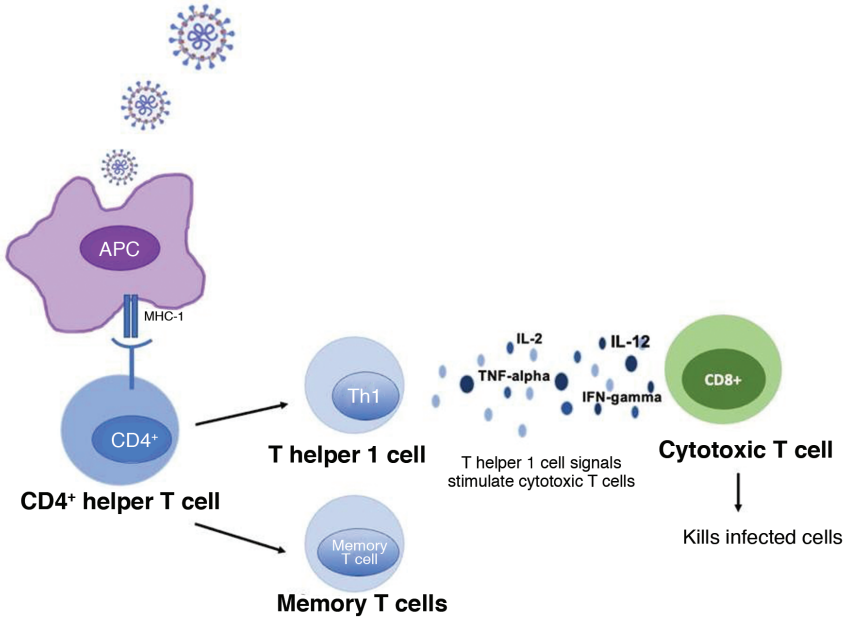

Figure 2. T cell mediated immune response against SARS-CoV-2.

still unclear. As an alternative pathway, the virus, which adheres to mucosal surfaces, can also infect the parts of the trigeminal nerve and the central nervous system (45). There are 3 nerves involved in the perception of taste in humans, and these cranial nerves are the facial nerve, vagal nerve, and glossopharyngeal nerve (46). This can be carried retrograde via the cranial nerves and cause neuroinflammation and/or neuroinfections in the human central nervous system. Although it is still not clear in some case studies and literature, the possibility of SARS-CoV-2 damage to these three nerves, which causes loss of taste, has been mentioned (43,44). The nerve endings of these cranial nerves are in the solitary tract. Since the solitary tract is close to the respiratory center, infection of the respiratory center may be the reason why some patients progress more severely than others (47,48).

Hematogenous Route

The blood-brain barrier and/or the blood-cerebrospinal fluid barrier, which are different layers that protect the brain, must be crossed in hematogenous dissemination for the disease to spread throughout the human central nervous system (43). In patients with COVID-19, IL-6 level is quite high compared to physiological conditions, and high IL-6 levels may affect the spread of the virus to the central nervous system by disrupting the integrity of the blood-brain barrier (49). There are 3 important mechanisms for spread through the blood-brain barrier: Transcellular spread (50), paracellular spread (51) and Trojan Horse (antibody dependent mechanism) (52). In addition, alveolar macrophages, which are monocyte-derived cells, carry the ACE-2 receptor, which is the receptor for the virus. Since there is active inflammation in the human lung, these cells can reach the central nervous system via blood (53). In the transcellular pathway, it may spread to the brain tissue as a result of infecting epithelial cells belonging to the blood-brain barrier (50). Immunohistochemical studies show that the ACE-2 receptor is found in all tissues of the human body. In paracellular pathway, on the other hand, it spreads between cells due to exogenous and endogenous factors, the integrity of the blood-brain barrier, that is, the destruction of adhesion bonds between cells (51). Another important mechanism in hematogenous spread is that non-neutralizing antibodies are infected with monocytes and/or lymphocytes and/or as a result of ineffective phagocytosis (52). As a consequence of ineffective phagocytosis of SARS-CoV-2, they can reach other tissues within the cell and infect in this way (53,54). Non-neutralizing antibodies may develop as a result of the inappropriate immune response against viruses. When non-neutralizing antibodies bind to the virus, they are phagocytosed by the antibody (55). The phagocytosed viruses are transported to peripheral tissues by immune cells (Figure 3) (55).

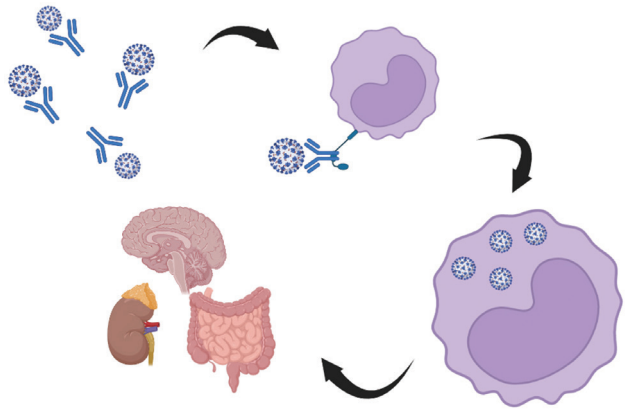

Figure 3. The mechanism of antibody dependent enhancement.

Digestive Tract Route

We have indicated that ACE-2, the SARS-CoV-2 cell entrance receptor, is not exclusively prevalent in respiratory epithelium (56). The ACE-2 receptor can also be found in intestinal cells (57) of the 1099 COVID-19 patients who experienced digestive problems (vomiting and diarrhea) (58). In a study using single cell RNA sequencing technology, it was discovered that the expression of the ACE-2 receptor in colon cells was inversely related to viral transcription, protein translation, humoral immunity, phagocytosis, and complement, and positively correlated with viral infection and innate and adaptive immunity (59). SARS-CoV-2 can interact with intestinal ACE-2, causing the epithelial cell barrier to be destroyed, the synthesis of inflammatory cytokines to be increased, intestinal absorption to be reduced, and the formation of intestinal mucosa to be increased (60). Furthermore, the inflammatory reaction might have deleterious effect on gut flora and trigger aggregation development (61,62). After replication, the virus may infiltrate local peripheral neurons and move to the CNS through its neurons (63). Herpes simplex viruses can migrate from the dorsal root ganglia to the nerve terminals of the enteric nerve system in the intestines (63). Although there is no clear evidence that SARS-CoV-2 may have entered the central nervous system retrogradely via the vagus nerve's digestive division, the compromised intestinal environment may have disrupted the integrity of the blood brain barrier via immunological, neurological, and humoral pathways, allowing the virus to access the central nervous system (63,64).

The Lymphatic and/or Cerebrospinal Fluid Pathways

There is a dense lymphatic network in the mucosal system of the human eye, mouth, and tracheal bronchi. Lymphatic networks belonging to the mucosal system can be invaded by SARS-CoV-2 (64-66). SARS-CoV, one of the

earlier variants of the virus, has been found in human and animal investigations to infect hilar lymphatic system and intestinal root lymph nodes (67,68). It has been shown that when peripheral lymph nodes are infected, SARS-CoV-2, is likely to enter the bloodstream and infect end organs (69). Brain tissue has its own circulation and selective membrane system to fulfill its physiological function. Under physiological conditions, cerebral solutes move along the glymphatic pathway in the interstitial fluid and cerebrospinal fluid (70). Cerebrospinal fluid from the subarachnoid space flows into the brain through the perivascular spaces and maintains osmotic balance with the interstitial fluid. This fluid movement enables the brain tissue to perform its physiological function (71,72). Brain tissue may develop brain edema in various pathological conditions. Including stroke, tumor, traumatic brain injury, and infections (73). One of the main causes of cerebral edema, which can cause serious damage to the morphology, structure and function of the brain, is viral infections (74). Disruption of this structure may also cause viral infectious agents to invade the brain tissue (75). This might mean that the virus penetrates into the brain through a compromised blood-brain barrier in severely and critically sick individuals, aggravating neurological symptoms, compromising awareness, and perhaps causing deleterious impact on cardiorespiratory region in the brain (76). In a case study, in a patient with acute necrotizing encephalitis due to SARS-CoV-2 infection, SARS-CoV-2 RNA was found in cerebrospinal fluid (CSF) after 19 days following the onset of symptoms after two PCR tests were reported as negative. He was determined to have an acute necrotizing encephalopathy linked to COVID-19. Despite the fact that the patient's CSF monocyte and protein levels were only minimally elevated and hence never entered a hyperinflammatory state, his cerebral function deteriorated to the point of coma (77).

Summary

When SARS-CoV-2 infects a human cell, a cellular and humoral immune response, which is a part of the innate immune system and adaptive immune system, is elicited. In the clinic of the disease, cytokine storms accompanying respiratory distress and systemic hypoxia can be seen in patients with severe cases. Such findings are likely to cause the virus to infect the brain. The virus's path to the brain may be primarily determined by the virus's transmission pathway and the location of its intracellular receptors. The vascular route to the brain is potentially fast, but it can only infect brain tissue if the illness has advanced to a certain point and the BBB is broken. Furthermore, neuronal retrograde transport is quite sluggish in the peripheral nerve channel. SARS-CoV-2 can infiltrate and grow quickly in olfactory sensory neurons. Furthermore, earlier research suggests that coronaviruses may infiltrate peripheral nerve terminals before entering the brain via a transsynaptic transfer. Given its proximity to the brain's center, the olfactory nerve pathway may be the primary route for the virus to reach the brain in the early stages of infection. To prevent the virus from contacting and infiltrating the human body, certain precautions, like wearing a mask and practicing hand cleanliness, as well as modern medical interventions, are needed. For early identification and quick care of neurological problems, clinical physical examination of the nervous system, detection of viral RNA in CSF, early antiviral medication, fast endotracheal intubation, and mechanical respiratory support should be indicated. Based on the consequences of the human corona-virus pandemic, long-term psychosocial and neurological rehabilitation should not be disregarded (78,79).

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Authorship Contributions

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