SARS CoV-2 Pathogenesis and Immune Response

Introduction

Coronaviruses (CoVs) are enveloped, positive-strand RNA viruses with large genomes (26-32 kb) (1). Some of the enveloped CoVs belonging to the large Coronaviridae subfamily that infect birds and mammals were known to cause self-limited infections in humans, mostly affecting the respiratory system. However, CoVs became important pathogens again as they caused serious outbreaks in the last 20 years, such as the severe acute respiratory syndrome CoV (SARS-CoV) in 2002 and the Middle East respiratory syndrome CoV (MERS-CoV) in 2012. In December 2019, the source of the epidemic, which was believed to be associated with seafood and wet animal market in Wuhan, China, was understood to be a new type of coronavirus, and on February 11, the World Health Organization (WHO) named the disease caused by the virus as COVID-19 (2). Molecular studies revealed that the new coronavirus belonged to the beta coronavirus group, and its sequence was 88% similar to two bat-origin SARS-like CoVs. (3). While initially it was named as 2019-nCoV, the International Commission on Virus Classification announced the name of this novel coronavirus as SARS-CoV-2. Due to a rapid spread of SARS-CoV-2 to many countries of the world and the increased mortality, WHO declared the COVID-19 outbreak an international health emergency in March 2020.
as a “pandemic” on March 11, 2020 (4). While most of the patients infected with SARS-CoV-2 had a mild clinical course, approximately 5% of the patients had severe lung damage or even multiple organ failure. Although it varies by country, the average death rate has been reported as 4%. (5). As of the end of June, 216 countries all over the world were affected by the epidemic, 10,021,401 people were confirmed to be infected with SARS-CoV-2, and 499,913 people died (6).

**SARS-CoV-2 Replication and Pathogenesis**

There are four main structural proteins in the structure of SARS-CoV-2: spike (S), envelope (E), membrane (M), and nucleocapsid (N) glycoproteins, as well as various accessory proteins (7) (Figure 1). Although the spike protein is located on the outer surface of the virus, it consists of two subunits. The S1 subunit plays a role in the binding of the virus to the receptor on the host cell surface, while the S2 subunit mediates cell fusion (8,9). S protein binds to the angiotensin-converting enzyme-2 (ACE-2) receptor of the host cell, and this complex is subjected to a proteolytic process by the host type II transmembrane serine protease (TMPRSS2) enzyme, and the virus enters the cell (10,11). The virus needs both ACE-2 and TMPRSS2 to enter the cell (12). A single-stranded positive-polar RNA with 5’ cap and 3’ polyA tail enters the cell. There are about 14 orf’s (open reading frames) encoding structural and non-structural proteins in this virus genome (13). First, this genomic RNA is broken down into small pieces by viral proteinases, and non-structural viral replicase polyproteins (pp1a and pp1b) are produced due to the translation of orf1 and orf2 genes. Polymerase enzyme synthesizes subgenomic sgRNA mRNA. Transmission of viral proteins also takes place from mRNAs. Finally, viral proteins and RNA genome combine within virions in the endoplasmic reticulum and Golgi body and are released into the environment as a result of the fusion of vesicles containing viral particles outside the cell with the cell plasma membrane (7) (Figure 2). At this stage, M protein plays an important role in stabilizing the N protein-RNA complex in the virion, keeping it together, and leaving the cell (13).

It is known that SARS-CoV-2 is transmitted by droplets, just like other human CoVs, and causes primary infection by binding to ACE-2 receptors that are abundant in lower respiratory tract epithelium. The mean incubation period was reported to be 4-5 days before the onset of symptoms, and 97.5% of symptomatic patients have symptoms within an average of 11.5 days (14). Typical manifestations of COVID-19 include fever and dry cough, although symptoms also include shortness of breath, muscle and/or joint pain, headache, diarrhea, nausea (5,15,16). Acute respiratory distress syndrome (ARDS) can be seen 8-9 days after the onset of symptoms in patients with severe COVID-19 (15,17). Biopsy and autopsy examinations of some COVID-19 patients have shown damage to the alveoli (18). Although the pathophysiology and virulence characteristics of the virus have not been clearly revealed yet, they are possibly related to the structural and non-structural proteins of the virus. Although many studies found ACE-2 receptors, which the virus binds in the small intestine, liver, kidney, and the central nervous system, no study has found viral particles in these organs.

**SARS-CoV-2 Immunopathology**

Host immune system develops various antiviral defense mechanisms against virus infections. Pattern recognition receptors (PRR) in host cells, especially Toll-like receptors (TLR) located in the cell, recognize RNA products formed during viral replication. As a result of this recognition, the immune system is activated by the secretion of type I interferon (type I IFN) from virus-infected cells (19). IFN suppresses protein synthesis in the infected cell by stimulating the RNA-dependent protein kinase enzyme, preventing viral replication and protecting uninfected cells against infection (20). Antigenic structures of pathogens are presented to CD8 T lymphocytes by antigen-presenting cells via MHC-I, and cytotoxic T-lymphocytes are activated with stimulation of cytokines interleukin ([IL]-12, IFN-α/β)). In addition, some dendritic cells can present the processed antigen to both CD4 and CD8 T-lymphocytes by phagocytosing the virus-infected cell (21).

The specific role of humoral and cellular immunity or innate immunity in relation to SARS-CoV-2 is not known, but it probably induces a similar immune response to SARS-CoV and MERS-CoV. RNA viruses are generally recognized by TLR-3.
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**Conclusion**

Although SARS-CoV-2 is in the coronavirus family, its pathophysiology has not been clearly understood yet. Studies on SARS-CoV2, which has become a pandemic in a short time in the world, often refer to the diagnosis and treatment options of the agent, but also include case reports. The number of patients in studies to explain the immune response, especially in COVID-19 patients, is very low. In order to fully and adequately explain the mechanism of immunopathogenesis, larger samples should be used. However, conducting research on virulence properties, intracellular mechanisms, immune stimuli, and escape mechanisms from the host immune response of SARS-CoV2 will bring a different perspective to approaches to the treatment of COVID-19 caused by the pathogen. Unfortunately, zoonotic viruses (Ebola, Zika, Dengue virus, West Nile Fever, MERS-CoV, SARS-CoV), including SARS-CoV-2, are serious threats today in a globalized world. Global warming may induce mutations in viruses by changing the habitat of viruses and their vectors. As a result of increased human mobility, the rapid spread of viruses through infected individuals has been seen again in the COVID-19 pandemic. In addition, it is noteworthy that bats, which are the only flying mammal and contain approximately 4,000 virus species, of which approximately 1,500 of these viruses are coronavirus, should be examined as a possible risk factor. Genomic research about mutations of viruses carrying potential risks is important to protect public health.

**References**


