

COVID-19: History, Etiology, Epidemiology, and Pathogenesis

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Abstract

The 2019 coronavirus disease (COVID-19) is an infectious disease caused by the virus SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2). The first case of the disease was identified in Wuhan, China, in December 2019. The disease quickly spread around the world as a pandemic.

COVID-19 is transmitted by breathing in air droplets and other small particles that contain the virus. Infection occurs most often when people are in close proximity, but it can also happen at greater distances between them, especially indoors. Spread of the disease can also occur by entry of contaminated fluids into the eyes, nose, or mouth, and less commonly through contaminated surfaces. Affected individuals carry the virus for up to 20 days and can spread it even if they do not develop the disease symptoms.

Keywords: COVID-19; SARS-CoV-2; RNA; S protein; M protein; N protein; antibodies; immune response; interleukins; lymphocytes; renin-angiotensin-aldosterone system.

1. Introduction

The virus of the disease COVID-19 has a natural animal origin. A joint study conducted in early 2021 by the People's Republic of China and the World Health Organization showed that the virus SARS-CoV-2 originated from another coronavirus that infected wild bats and, after mutation, transferred to humans. According to articles published in July 2022 in *Science*, the transmission of the virus to humans occurred in November 2019, possibly during the trade of live wild animals at the wet market in the city of Wuhan (Hubei, China). However, there are also hypotheses that the virus may have been accidentally released from an experimental virology laboratory. The first human infections were identified in December 2019 in Wuhan, and in January 2020 the first 41 cases of confirmed COVID-19 cases were published in *The Lancet*.

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2. Etiology

The causative agent of COVID-19 is the SARS-CoV-2 coronavirus (Figure 1). It was first isolated from pneumonia patients in Wuhan. Its thousands of variants, according to WHO guidelines, are denoted by letters of the Greek alphabet: alpha, beta, gamma, delta, and omicron.

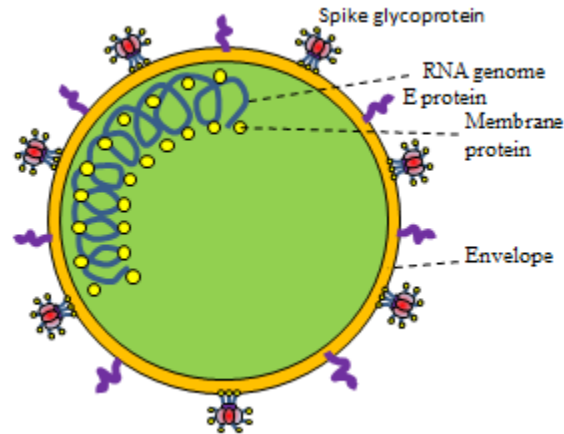


Figure 1: Construction of SARS-CoV-2.

Each SARS-CoV-2 virion is 60–140 nm in diameter. Like other coronaviruses, it has four structural proteins known as spike protein S, envelope protein E, membrane protein M, and nucleocapsid protein N. The S, E, and M proteins together form the viral envelope.

The S protein is a glycoprotein, composed of two subunits: S_1 and S_2 . It binds to the ACE2 receptors on the plasma membrane of the host cell – S_1 subunit catalyzes the attachment and S_2 subunit helps in the fusion of the virus with the host cell. Studies have shown that the S_1 subunit induces high levels of IgG and IgA antibodies. The M protein is responsible for the transmembrane transport of nutrients. It causes bud release by the host cell and takes part in the formation of the viral envelope.

The N-protein is associated with the RNA genome of the virus.

3. Viral genome

SARS-CoV-2 possesses a linear positive single-stranded RNA genome of about 30,000 bases in length. It contains 32.2% uridine (U), 29.9% adenosine (A), 19.6% guanosine (G), and 18.3% cytidine (C). Viral variants arise through mutations, in which guanosine and cytidine convert to build adenosine and uracil, respectively. The mutation of the CG-dinucleotides is thought to avoid the zinc finger of an antiviral protein defense mechanism of cells [1].

To date, millions of SARS-CoV-2 genomes were sequenced and many are added every month.

4. Epidemiology

Infectious particles are much smaller than the exhaled aerosol, which remains in the air for a long time. Aerosol droplets can be inhaled or get on the mucous membranes of the eyes, nose, or mouth. When people are physically close, air droplets transmit the viruses more easily, but it also can be transmitted over greater distances between them, mainly in places that are poorly ventilated. The small particles can remain in the air minutes to hours.

Pets, especially cats, can also get COVID-19. In them, the disease manifests itself with cough and digestive symptoms. Cats can spread the virus to other cats or to people. Dogs are less susceptible to this infection. The pets also can transmit the disease to humans by kissing and petting the animal. Monkeys, for example, orangutans, also can be infected with COVID-19. The virus does not appear to be able to infect pigs, ducks, or chickens.

5. Pathogenesis

The immune response of human against SARS-CoV-2 virus is mixed: cell-mediated immunity and antibody production (Figure 2). After virus invasion, B-cells interact with T-cells and begin to divide to form plasma cells that produce antibodies (immunoglobulins). Since SARS-CoV-2 has been in the human population since December 2019, it remains unknown whether immunity is long lasting in people who recovered from the disease. The presence of neutralizing antibodies in the blood corresponds to the protection from infection, but their concentration decreases fourfold after one to four months after the onset of symptoms. Memory B cells specific for the spike and nucleocapsid proteins of SARS-CoV-2 persist in the body for at least six months after the onset of symptoms. If the virus invades the human organism again, the memory cells quickly produce new antibodies against the SARS-CoV-2.

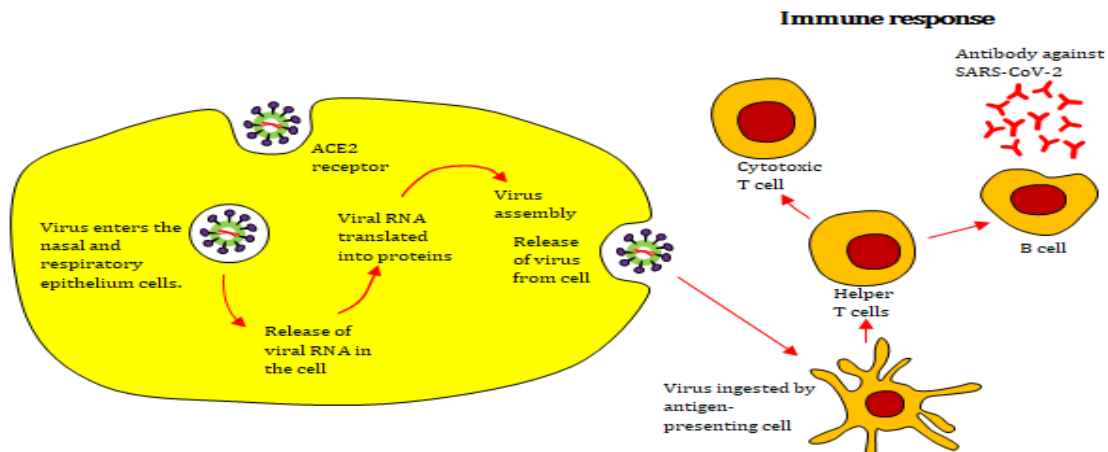


Figure 2: Key components in the immune response against SARS-CoV-2.

During the pathogenesis of the disease, following processes take place: B-cells synthesize antibodies that neutralize

the virus; cytotoxic T-cells using their granzymes, perforin, and interferons kill virus-infected cells; and helper T₁ and T₂ cells through their interleukin 1 and interferons suppress the inflammation that has occurred.

In COVID-19, increased concentrations of interleukins IL-1, IL-2 and IL-7, granulocyte macrophage colony-stimulating factor (GM-CSF), interferon-induced γ -protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha (MIP-1 alpha), and tumor necrosis factor (TNF) are established.

Interleukin 1 (IL-1) occurs in two forms – α and β . They bind to a same receptor. IL-1 activates T- and B-lymphocytes. In addition, it stimulates macrophages to express surface receptors for gamma interferons. Thanks to this, it increases their phagocytic activity.

Interleukins (IL) are synthesized by both CD4⁺- and CD8⁺ T-lymphocytes after interaction with specific antigens. They bind to specific receptors on the plasma membrane of certain cells. Interleukins are responsible for the interactions between cells in the connective tissue, nervous system, skin and other organs. Therefore, they regulate not only local and systemic immune processes, but also wound healing, hematopoiesis and other biological processes, as well as the course of inflammatory and allergic processes.

Interleukin 2 (IL-2) is synthesized by helper T-lymphocytes 1 (TH₁ cells). It has a relative molecular mass M_r of 15,000. IL-2 activates macrophages and is a mitogenic factor for T-lymphocytes – they do not proliferate in the absence of IL-2 even after contact with an antigen-presenting cell. In addition, interleukin 2 stimulates B-cell proliferation and the synthesis of IgM and IgG₂.

Interleukin 7 (IL-7) is a glycoprotein with $M_r = 25,000$. It is secreted by stromal cells in the bone marrow. Together with SCF (stem cell factor), IL-7 acts as a growth factor for the precursors of T- and B-cells.

Alpha-interferon promotes the elimination of infected cells, and in addition regulates the expression of ACE-2, thus facilitating the entry of the virus into cells.

Systemic inflammation leads to vasodilation, which allows inflammatory lymphocytic and monocyte to infiltrate the lung and heart. In particular, pathogenic GM-CSF-secreting T-cells have been shown to correlate with the recruitment of inflammatory IL-6-secreting monocytes and severe lung pathology in humans with COVID-19.

6. SARS-CoV-2 and the renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) synthesizes a cascade of vasoactive peptides that regulate key processes in human physiology. It possesses ACE2 receptors, which physiologically inhibit the RAAS activation [2,3]. The SARS-CoV-2 virus interacts with the ACE2 receptors of RAAS (Figure 3). The infectivity of the coronavirus is due to this interaction [4,5]. There are opinions according to which the use of ACE-inhibitors and angiotensin receptor blockers should stop this process.

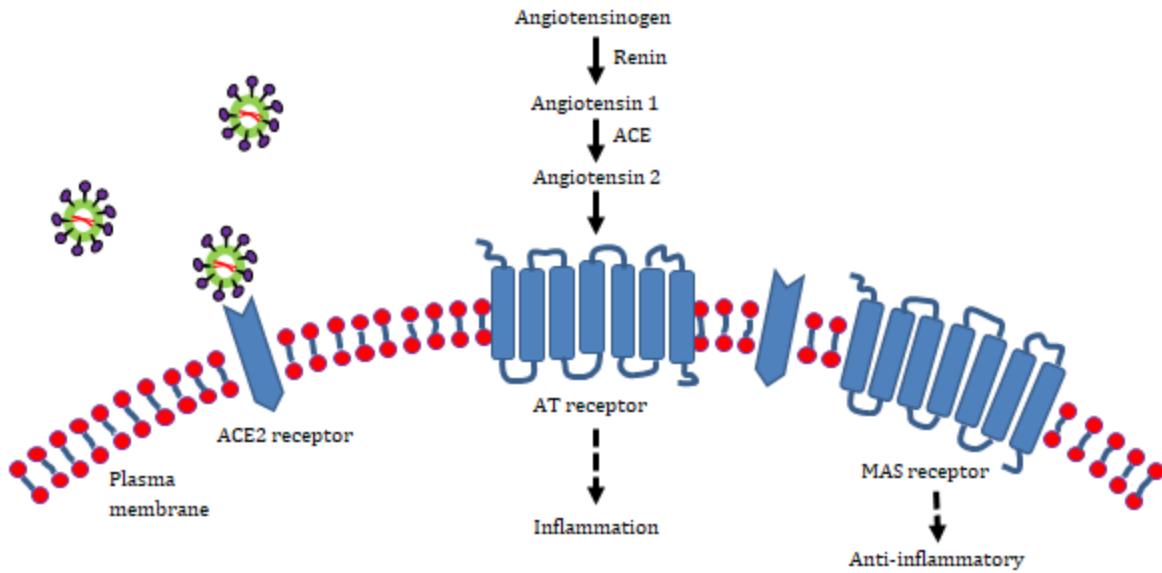


Figure 3: Relationship between SARS-CoV-2 and the renin-angiotensin-aldosterone system.

The effect of coronavirus on ACE2 results in leukocyte infiltration, increased permeability of the blood vessels and alveolar wall, and decreased secretion of pulmonary surfactants. These reactions cause most of the respiratory symptoms. The worsening local inflammation causes a cytokine storm, ultimately leading to a systemic inflammatory response syndrome.

7. Immune response

The immune response of patients with COVID-19 is complex: cellular and antibody[6]. After the virus enters the body, B-lymphocytes interact with T-lymphocytes and transform themselves into plasma cells that synthesize antibodies (immunoglobulins) against the virus. It is not yet known how long this immunity lasts after passing the disease [7].

Virus-neutralizing antibodies can be detected in the blood, but their concentration decreases over time. It is believed that their concentration decreases four times in one to four months after the onset of disease symptoms. Memory B cells, specific for the spike and nucleocapsid proteins of SARS-CoV-2, persist for at least six months after the symptoms onset. Upon re-entry of SARS-CoV-2, antibodies rapidly are synthesized.

About 35% of healthy adults who were not exposed to SARS-CoV-2 have CD4⁺ T cells. These cells recognize the S-protein (its subunit S₂) of SARS-CoV-2 virus. It is not known whether different people use similar antibody genes during COVID-19.

The severity of COVID-19 depends on the concentration of the cytokines. When their concentration (of IL-1, IL-2,

IL-7, α -TNF, γ -interferon, and chemokines) is very high, an acute inflammation known as a cytokine storm is observed [8].

Cytokine storm underlies an acute hyperinflammatory response that can cause multiple organ failure [9]. acute pulmonary failure, stroke, myocardial infarction, encephalitis, acute kidney injury, and vasculitis.

Cells of the central nervous system (microglia, neurons and astrocytes) also take part in the release of cytokines. Therefore, the CNS also is often affected. These severe pathological manifestations can cause death.

8. Conclusions

COVID-19 is a pandemic disease, worldwide spread in and after 2019. It has damaged many lives on Earth and is still a big danger for the manhood. The scientists have already established the etiology and pathogenesis of COVID-19 and have found some treatment methods for it.

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