

Virology, Immunity and Vaccine Development of SARS-CoV-2

Sidre Erganiş¹  Gülendam Bozdayı² 

1 Kars Harakani State Hospital, Department of Medical Microbiology, Kars, Turkey

2 Gazi University Medical Faculty, Department of Medical Microbiology, Division of Medical Virology, Ankara, Turkey

Abstract

Since the last months of 2019, the COVID-19 pandemic caused by SARS-CoV-2, a brand new coronavirus, catches our attention on our agenda as it harms economic and socio-cultural structures almost all around the world. For the elimination of SARS-CoV-2, there has to be an effective and sufficient immune response that includes innate and adaptive immunity against the virus. Also, this immunity should help us to prevent and control the infection. However, there are some complications about our body's response to this virus: Hyperactivation of the immune response can cause tissue damage and organ failures. On the other hand, immunodeficiency is one of the major obstacles to the elimination of the virus. Type I IFN response is essential for COVID-19 disease. Some of the SARS-CoV-2 infection pathogenesis is caused by delay, deficiency, or inhibition of IFN release. The infection can be limited if type I IFN is secreted early and adequately. The overproduction of pro-inflammatory cytokines (such as IL-1, IL-6, and TNF α), neutrophilia, and lymphopenia is associated with COVID-19 disease severity and mortality in patients. Our current understanding of SARS-CoV-2 immunity is still limited. Further clarification of the immunopathogenesis of COVID-19 disease will guide us in both diagnosis and treatment. It will also shed light on new drugs and vaccine studies. Therefore, extensive researches on the host immune response against SARS-CoV-2 are still necessary.

Key words: COVID-19, Immunity, SARS-CoV-2 Vaccine.

INTRODUCTION

Coronaviruses (CoV) are zoonotic agents that can infect many animals and humans in nature. They are common viruses that usually cause respiratory tract infections. Although human coronaviruses (HCoV)-NL63, HCoV-229E, HCoV-HKU1 and HCoV-OC43 mostly cause self-limiting upper respiratory tract infections, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and

Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) can cause fatal respiratory disease in humans. They may also cause various clinical diseases with gastrointestinal, hepatic, and neurological involvement (1-3).

Although the diseases caused by coronaviruses in humans did not attract much attention before, they have become quite popular in the last two decades. Outbreaks caused

Cite this article as: Erganiş S, Bozdayı G. Virology, Immunity and Vaccine Development of SARS-CoV-2. Arch Curr Med Res 2021;2(1):05-13

Corresponding Author:

Sidre Erganiş, Kars Harakani State Hospital, Department of Medical Microbiology, Kars, Turkey
E-mail: sdrerganis@gmail.com



Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

by SARS-CoV in 2002 and MERS-CoV in 2012 have attracted considerable attention due to the high mortality rates (3). The first SARS case was reported in China in November 2002. SARS affected 26 more countries, causing a total of 8096 cases and 774 deaths. As of July 2003, the World Health Organization (WHO) declared the end of the SARS outbreak, and no human SARS cases have been identified since then. MERS-CoV was first reported from Saudi Arabia in 2012; it had a high mortality rate (34%), mostly caused by acute pneumonia and renal failure. MERS-CoV caused 2562 cases and 881 deaths worldwide at the end of December 2020 (4, 5). A brand new coronavirus with a mortality rate of 2% has been on our agenda because it has damaged economic and socio-cultural structures almost everywhere in the world by causing a pandemic at the beginning of 2020 (3, 6).

In December 2019, cases of pneumonia of unknown cause were detected in people who had a connection with the seafood and livestock market in the Wuhan province of China. The authorities reported that the authorities in China to WHO, on December 31, 2019, that the agent causing the disease may be a new virus epidemic factor. With the full genome analysis of the virus, it was found on January 7, 2020, that the agent was a new coronavirus, and it was very similar to SARS-CoV (80%). The new virus was named SARS-CoV-2, and the disease it causes was named COVID-19. Due to the rapid spread of the disease worldwide, WHO declared a pandemic on March 11, 2020 (7). Despite many measures taken, by the end of 2020, more than 75 million people worldwide were diagnosed with COVID-19, and around 1,7 million people died due to COVID-19 (8). According to Turkey's Ministry of Health data, approximately 2.2 million people were infected with SARS-CoV-2, and 19371 people lost their lives due to COVID-19 on December 25, 2020 (9). These numbers are increasing day by day.

Antiviral drug and vaccination studies are continuing in almost all countries against SARS-CoV-2. An antiviral with a curative effect against COVID-19 has not been found yet. However, some vaccines that have completed the pre-clinical phase or phases 1-3 are ongoing, and they are promising for the future (2, 10-12). There are currently 61 vaccine candidates in the clinical phase 1-3 and 172 in the pre-clinical phase (13).

VIROLOGICAL FEATURES OF CORONAVIRUSES

Coronaviruses (CoV) are enveloped, positive-sense single-stranded RNA viruses that belong to the Coronavirinae subfamily in the Coronaviridae family in the Nidovirales order. The Coronavirinae subfamily includes four genera: alpha-CoV (α CoV), beta-CoV (β CoV), gamma-CoV (γ CoV) and delta-CoV (δ CoV). According to evolutionary analysis, it has been shown that α CoV and β CoV are of bat and rodent origin, and γ CoV and δ CoV are of bird origin. Among these four genera, only the α CoV and β CoV strains are known to infect humans. There are seven coronaviruses known to cause infections in humans. Among these, HCoV-229E (229E) and HCoV-NL63 (NL63) belong to the α CoV genus; HCoV-HKU1 (HKU1), HCoV-OC43 (OC43), SARS-CoV, MERS-CoV, and SARS-CoV-2 belong to the β CoV genus (1, 2).

Structural features of SARS-CoV-2

1. Genome

The genome of coronaviruses is approximately 30 kb and is the most extensive known RNA among viruses (4, 5). The SARS-CoV-2 genome ranges from 29.8 kb to 29.9 kb and has 11 open reading regions (ORF). The ORF lab gene region at the 5' end, which makes up approximately 66% of the genome, encodes 16 non-structural proteins (nsp). The rest of the genome, the 3' end, contains genes encoding four structural (S, E, M, and N) proteins and contains ORF3a, ORF6, ORF7a, ORF7b, and ORF8 genes that encode six accessory proteins. (2, 14).

2. Envelope

The envelope is comprised of; spike (S) protein, membrane (M) protein, and envelope (E) protein.

Spike proteins protrude out of the envelope, and this structure has given its name to coronaviruses because it resembles a crown (corona) structure. The virus acts by binding to host cells with its homotrimeric pointed glycoprotein structure, making this protein a crucial target for potential diagnosis and treatment. SARS-CoV-2 attaches to the host cell's ACE-2 (Angiotensin-converting enzyme-2) receptor with its S proteins to enter the host cell. Meanwhile, transmembrane serine protease-2 (TMPRSS2) is involved in preparing the S protein (2, 15). S protein has two subunits: S1 and S2. The primary function of the S1 protein is to bind to

the host cell receptor. This binding also triggers the fusion of the viral membrane and the host cell membrane. S2 protein is mainly responsible for the fusion of membranes. There is a furin cleavage region (PRRAR) on the border between S1 and S2 subunits. Furin is an enzyme mostly expressed in the lungs that play a role in viral infections. Furin has the potential to increase the fusion between the viral membrane and the host cell membrane by cleaving envelope glycoproteins (2, 16).

The S protein binds to ACE-2 via its receptor-binding domain (RBD) (2). It is known that with the D614G mutation, amino acids on RBD are altered (glycine instead of aspartic acid), and this polymorphic virus has been reported to become dominant in the world. It has been suggested that this D614 mutated variant causes an excessive viral load in the upper respiratory tract and increases the virus's contagiousness; however, it does not aggravate the presentation of the disease. Nevertheless, the clinical significance of this variant is not fully known(17). On December 14, 2020, authorities from the United Kingdom of Great Britain and Northern Ireland reported that a new SARS-CoV-2 variant was identified with viral genomic sequencing. This new variant was referred to as SARS-CoV-2 VUI 202012/01 (Variant Under Investigation, the year 2020, month 12, variant 01). Initial analysis was reported to indicate that this new variant may spread easier than its predecessor among humans. The variant is defined by the presence of a range of 14 mutations that resulted in some amino acid changes and three deletions. It is thought that some of these mutations may alter the transmissibility of the virus in humans. Two of the identified mutations are N501Y and P681H mutations in the RBD. Research is ongoing in order to determine whether this variant is associated with any changes in symptom severity, antibody response, or vaccine efficacy (18).

The M protein has three transmembrane domains. It gives shape to virions, enhances the curvature of the membrane, and binds to the nucleocapsid. The E functions in both virus assembly and secretion, and it plays a role in the pathogenesis of the virus (19).

3. Nucleocapsid (N) protein

N protein is associated with the RNA genome of SARS-CoV-2. It protects the genome and preserves the viral

RNA stability by shaping its structure(2). N protein has two domains, which has the ability to bind the viral RNA genome through various mechanisms. It has been reported that N protein can attach to nsp3 protein to help bind the virus genome to RTC, and package the encapsidated genome into virions. It also inhibits host cell interferon (IFN) synthesis and secretion during viral replication(19).

PATHOGENESIS

The characteristics of the virus and the host play a significant role in developing the COVID-19 disease and determining the clinical severity of the disease. The viral load, the characteristics of the virus mutation, the viral escape mechanism of the virus, and the age, gender, neuroendocrine-immune regulation, and HLA genes of the host affect the disease's course (20).

SARS-CoV-2 is mainly transmitted through respiratory droplets and various contact routes. Therefore, the virus spreads easily in overcrowded areas. The virus first begins to replicate in the nasal cavity and pharynx, then progresses to the lower respiratory tract. Binding of the virus to a host cell by the target ACE-2 receptor is the first step of SARS-CoV-2 infection. ACE-2 is a carboxypeptidase that converts angiotensin I to angiotensin II. It is expressed in many places in the body, such as the nose, lung, ileum, heart, eye, liver, bladder, kidney, pancreas, brain, prostate, testis, and placenta. Thus it causes many different clinical situations and multiple organ dysfunction. SARS-CoV-2 is inclined to infect airway and alveolar epithelial cells, vascular endothelial cells, macrophages, and type 2 pneumocytes by binding to the ACE-2 receptor (3, 20). Especially binding of SARS-CoV-2 to receptors in type II pneumocytes (ACE-2) in the lungs triggers an inflammatory cascade in the lower respiratory tract, which is among the cornerstones of the pathogenesis (21).

While the S1 subunit binds to ACE-2 with its RBD, furin protease catalyzes the cleavage formation between the spike proteins (S1 / S2), and S2 subunit binds to TMPRSS2 of the host cell for the virus to fuse to the host cell membrane (22). The virus then enters the host cell, and the genome of the virus is released into the host cell cytoplasm. The replicase transcriptase complex is formed directly from the positive RNA genome, and the

RNA replication begins. In coronaviruses, this complex is only responsible for viral RNA synthesis; thus, it is able to escape the immune system response. After translation of structural and accessory proteins, the M, S, and E proteins attach onto the endoplasmic reticulum membrane. The mature virion is formed when the nucleocapsid and viral genome reach the Endoplasmic Reticulum - Golgi intermediate compartment (ERGIC). After the assembly, virions are transported to the surface of the cell in vesicles and released by exocytosis (3, 23).

Recently, many studies also indicate that SARS-CoV-2 penetrates host cells using CD147-spike protein. It was mentioned that this novel invasion route for SARS-CoV-2 could provide a new target for antiviral drug development. However, as these results are controversial, further research is needed (24-26).

COVID-19 infection becomes symptomatic after an incubation period of approximately 5.2 days. The most common symptoms are fever, dry cough, weakness, and dyspnea because the virus primarily targets the airways. Other symptoms of the disease include sputum production, headache, diarrhea, and lymphopenia. The patients' clinical situation is asymptomatic or mild in most patients. The disease progression worsens in about 10-20% of the patients, which have to be followed up in the hospital service or an intensive care unit. Among the risk factors for poor prognosis, comorbidities such as advanced age, male gender, obesity, hypertension, cardiovascular disease, diabetes, and respiratory system disease may be listed (3, 27).

COVID-19 pneumonia is atypical viral pneumonia. Although histopathological findings are non-specific, they are important. Pathological changes associated with COVID-19 are usually encountered in the lungs. These changes generally include bilateral edema, protein or fibrin-rich alveolar exudate, diffuse reactive hyperplasia of type II pneumocytes with widespread alveolar damage, desquamation of pneumocytes, and hyaline membrane formation (21, 28).

The pandemic still continues, and more information is needed on the virus's life cycle and host's immune response to find effective treatment options and vaccines for the COVID-19 disease (3).

IMMUNE RESPONSE TO SARS-COV-2

SARS-CoV-2 has been shown to disrupt normal immune system responses, causing uncontrolled inflammatory reactions in severe and critical COVID-19 patients. It is known that these patients have lymphocyte activation, lymphopenia, lymphocyte dysfunction, granulocyte and monocyte abnormalities, high cytokine levels, and an increase in total antibodies (29).

Innate Immune Response

The innate immune response constitutes the first line of host defense against the coronavirus infection and is important in immunity against viruses. It consists mainly of macrophages, dendritic cells, natural killer (NK) cells, and molecules such as type I interferon (IFN), cytokines, and chemokines (30).

In RNA viruses such as SARS-CoV-2, this immune response begins with the recognition of single and double-stranded viral RNA (ssRNA, dsRNA, respectively) by pattern recognition receptors (PRRs). Phagocyte cells with PRRs on their surfaces become activated when pathogen-associated molecular patterns (PAMPs) expressed by pathogens are recognized. PRRs important for coronavirus are toll-like receptor (TLR) 3 and TLR7, which are activated by RNA in endosomes; RIG-I (retinoid-inducible gene) / MDA-5 (melanoma differentiation-associated gene 5) and the cGAS-STING pathway, which recognize cytosolic RNA (31, 32). This recognition event leads to the synthesis of cytokines via Nuclear Factor kappa B (NF- κ B) and interferon regulatory transcription factor (IRF3) pathways (32). Among these cytokines, there are type I (IFN- α , β , ω) and type III (IFN- λ) interferons, which are the most critical elements of the antiviral response. There are also pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF - α), interleukin-1 (IL-1), IL-6, and IL-8. These induce the antiviral immune response in target cells and enhance the acquired antibody response. Type I IFN response is particularly important. The fundamental pathology in SARS-CoV-2 is a delay, deficiency, or inhibition in IFN release. SARS-CoV-2 infection can be limited if type I IFN is secreted early and properly. Type I IFN triggers an antiviral effect by inducing interferon-stimulated genes (ISGs), which have the ability to inhibit viral replication to an extent

through various mechanisms. Suppose there is a delay in IFN production. In that case, viral replication cannot be controlled; cellular damage occurs in the airway epithelium and lung parenchyma, resulting in the formation of a lethal inflammatory cytokine storm. These cases are generally more common in older people (31).

The data obtained from various studies suggest that a myeloid response disorder may contribute to acute respiratory distress syndrome (ARDS), cytokine storm, and lymphopenia development in patients with severe COVID-19. It has been shown that monocyte-derived inflammatory macrophages (FCN1 + macrophages) were increased in bronchoalveolar lavage (BAL) samples in severe COVID-19. FCN1 + macrophages have an inflammatory and cause excessive chemokine production seen in the cytokine storm (33).

It is thought that the dysregulated macrophage activation observed during a coronavirus infection, parallel to the significant macrophage infiltration to the lungs, plays a part in the pathogenesis of severe COVID-19 cases. According to RNA sequence analysis, 80% of the total cells in bronchoalveolar lavage fluid (BALF) of severely ill patients are mononuclear phagocytes (MNPs), and it is known that most of the MNPs in BALF are monocyte-derived macrophages rather than alveolar macrophages (30).

Neutrophils are the first line of cells that reach the site of infection and destroy pathogens through oxidative burst, phagocytosis, cytokines, proteases, and neutrophil extracellular traps (NETs). NETs are web-like DNA structures and proteins that are secreted from neutrophils. NETs are useful in host defense against pathogens; however, the continuous formation of NETs causes damage to epithelium, endothelium and acts as a stimulating factor for many diseases. Neutrophilia occurs in severe COVID-19 patients. It is argued that the increase in NETs formation may be related to some genes. The excessive NETs formation may induce consecutive inflammatory reactions that destroy the surrounding tissues, cause micro thromboses and result in permanent organ damage to the pulmonary, cardiovascular, and renal systems (34, 35). Besides, an increased neutrophil/lymphocyte ratio has been determined to be an independent risk factor for severe disease (35).

The complement system plays an important part in the immune reaction against viral infections. It participates in acute lung injury whilst the coronavirus infection. A recent study examining the histology of pulmonary and cutaneous biopsies and autopsy samples from five critical patients infected with SARS-CoV 2 revealed complement-mediated micro thrombotic disease, including c5b-9, c4d, and Mannan-binding lectin serine protease 2 (MASP2) deposits. The use of an anti-C5a antibody in a mouse model of MERS-CoV infection resulted in the recovery of the respiratory symptoms without an increase in the viral load (3).

There are studies reporting a decrease in NK cell count in peripheral blood in patients with severe COVID-19. CXCR3 is a chemokine receptor that mediates NK cell infiltration. In vitro, CXCR3 ligand (CXCL9-11) has been observed to increase in the lung tissue of patients infected with SARS-CoV-2 and the proliferation of monocytes producing CXCR3 ligand in the lung of COVID-19 patients. The CXCR3 pathway is thought to facilitate the uptake of NK cells from the peripheral blood into the lungs in COVID-19 patients. Besides, impaired production of chemokine, IFN- γ , and TNF- α was detected in these cells. Significant increases in NK cell inhibitory receptor NKG2A expression were observed in patients infected with SARS-CoV-2. NKG2A expression induced by SARS-CoV-2 may be associated with early functional depletion of cytotoxic lymphocytes such as cytotoxic T lymphocytes and NK cells, leading to disease progression (30, 31).

Adaptive Immunity

1. Cellular Immune Response

Lymphopenia is a key feature of COVID-19 patients, and it happens mainly in severe cases. Significant decreases in CD4+ T cell, CD8+ T cell, NK cell, and B cell numbers are observed. It is known that lymphocyte percentages are below 20% in severe cases. Previous research has revealed a notable reduction in T cell counts, specifically CD8+ T cells, in severe cases compared to mild cases. It has been reported that the lymphopenia level, especially T lymphocyte levels, can be a predictor for the severity and prognosis of the disease and risk of death (29). The mechanism of lymphopenia in COVID-19 infection is

still unknown; however, some possible explanations for this finding have been provided, including chemokine-mediated redistribution, virus-induced destruction, bone marrow suppression, and apoptosis (30).

Lymphocytes are activated but dysfunctional in COVID-19. In a study of 128 patients who recovered, CD8+ T cell response was observed more frequently than the CD4+ T cell response. Zhou et al. reported that CD69, CD38, and CD44 surface receptors on CD4+ and CD8+ T cells were highly expressed in SARS-CoV-2 infected patient group in contrast to the healthy control group. OX40 and 41BB are critical molecules in the clonal expansion and stimulation of the immune response. These molecules were significantly increased, indicating T cell activation, especially in severe COVID-19 patients. Besides, T cells in COVID-19 patients indicate depletion of phenotypes, highly elevated exhaustion levels, and decreased functional diversity of T cells, which may be considered a marker for severe disease progression in COVID-19 patients (29).

2. Humoral Immune Response

It is believed that SARS-CoV-2 creates a potent B cell response, which is dependent on detection of virus-specific IgM, IgG, and IgA and neutralizing IgG (nAb) after a patient has been infected (36). After the onset of symptoms, IgM and IgA can be detected on 5-7th days, and IgG on 7-10th days in blood. Mostly serum IgM and IgA titers begin to decrease at nearly 28 days, and IgG titers peak at approximately 49 days (37). It is still not fully understood exactly how long IgG titers remain high in the blood; thus, further studies are needed to enlighten this subject.

The most commonly detected antibodies are the ones that bind to S and N proteins. However, among the four structural proteins of coronavirus, S protein is believed to be the only active antigen that triggers the production of neutralizing antibodies (30). The primary target of neutralizing antibodies (nAb) in SARS-CoV is the receptor-binding domain (RBD) of the S protein, which binds to the ACE-2 receptor. This region is highly immunogenic. Antibodies that bind to this domain neutralize and block the virus interaction with the host entry receptor ACE2 (31).

It is believed that the antibody-dependent enhancement (ADE) phenomenon may cause severe clinical COVID-19 cases. It has been documented that ADE occurs in viral infections by two different mechanisms. The first mechanism increases antibody-mediated virus uptake into phagocytic cells by Fc gamma receptor IIa (FcRIIa); thus, viral replication also increases. The second mechanism increases inflammation through excessive amounts of antibodies that form an immune complex. Both mechanisms function through non-neutralizing antibodies and/or antibodies at sub-neutralizing levels that bind to viral antigens without directly inhibiting or removing the infection (38). Clinical deterioration associated with ADE is well described in some viral infections such as Dengue, Zika, Ebola, and MERS. A neutralizing monoclonal antibody targeting the RBD of the S protein of the MERS virus has been proven to promote virus entry into cells via the Fc portion of the antibody that binds to the Fc receptor (FcR) on cells. This information supports the relationship between antibody upregulation and the poor prognosis of patients infected with the SARS-CoV-2 virus. However, the ADE-mediated inflammatory response and the association of preexisting antibodies with disease progression and severity in COVID-19 patients require further research (29, 36).

VACCINES FOR COVID-19

A strong consensus worldwide that a COVID-19 vaccine will probably be the most effective way to control the COVID-19 pandemic (39) sustainably. Vaccine development fit for human use may take years, mainly if new technologies that have not been broadly tested for safety or scaled up for mass production are being used (40). Nevertheless, a remarkable research effort and global coordination have resulted in the fast development of vaccine candidates and initiated various trials (39).

Moreover, previous research on SARS-CoV and the related MERS-CoV vaccines have shown that the S protein on the virus surface is an ideal target for a vaccine. In both viruses, SARS-CoV and SARS-CoV-2, the S protein interacts with the ACE2 receptor, and antibodies that target the S protein may interfere with this attachment, thus neutralizing the virus. Therefore, the S protein has been the major target for vaccine development (40). The advantages and disadvantages of the different strategies vaccines are summarized in Table 1.

Table 1. The overview of the different vaccine production process (40, 41)

| Vaccine Type | Target | Advantages | Disadvantages |
|--------------------|--------------|---|--|
| Live attenuated | Whole virion | Existing infrastructure can be used, induce immunity higher | Production infectious material, takes time because of large genome size, inappropriate for highly immunosuppressed patients |
| Inactivated | Whole virion | Existing infrastructure can be used, safety, adjuvants can be used to increase immunogenicity | The need for large amounts of infection virus, antigen and/or epitope integrity needs to be confirmed |
| Subunit | S protein | High safety, adjuvants can be used to increase immunogenicity | Global production capacity might be limited, antigen and/or epitope integrity needs to be confirmed, high price, lower immunogenicity, require adjuvants and several doses |
| Viral vector-based | S protein | Safety, induces high titer immunoglobulins, excellent pre-clinical and clinical data for many emerging viruses, including MERS-CoV | Vector immunity may affect vaccine effectiveness conversely |
| RNA | S protein | No infectious virus needs to be handled, vaccines are usually immunogenic, rapid manufacturing possible | Safety issues with reactogenicity have been reported |
| DNA | S protein | No infectious virus needs to be handled, low production costs, high heat stability, tested in humans for SARS-CoV, rapid manufacturing possible | The vaccine needs specific delivery devices to reach good immunogenicity |

Licensed vaccines used in humans are traditionally live attenuated viruses, inactivated viruses, protein or polysaccharide conjugated subunit, and virus-like particles vaccines. Several new technologies have been introduced in vaccine development in recent years, such as nucleic acid (DNA and RNA), viral vector, and recombinant protein-based vaccines (39).

The classical inactivated viral vaccine could be produced with chemical and physical agents such as formaldehyde, UV light, and β -propiolactone. Whole virus vaccines have a significant advantage compared to other vaccines because they have the ability to induce more effective than the different vaccine types. However, live virus vaccines should be investigated more carefully because of the safety issues (41).

Vector vaccines are usually constructed with a carrier virus such as an adenovirus or smallpox virus. The virus used is non-replicative. The carrier virus is designed to carry the S gene of SARS-CoV-2. The main advantage of vector vaccines; it has the ability to induce potent T cell responses without the need for an adjuvant (42, 43).

Different types of subunit vaccines are developed and studied, such as recombinant production of the S protein. One vaccine consists of a trimerized SARS-CoV-2 S protein, and another one only contains the receptor-binding domain (RBD) (41). Subunit vaccines in which the proteins of the virus are injected into the host have the potential to exhibit efficacy in protecting humans from viral infection. However, given that only a few viral components of the virus are included in the vaccine, their protective efficacy

may be limited, and in some cases, they can cause unstable immune responses (43). Also, unlike viral vector vaccines or nucleic acid based, recombinant S proteins in subunit vaccines may have an appropriate epitope structure unless they are produced in mammalian cells (42). Virus-like particles (VLP) vaccines have viral capsid proteins but do not have a genome. Therefore, it is safe and causes a high immune response (43).

The traditional vaccine production process is very time-consuming for responding to an outbreak. In contrast to traditional vaccines, nucleic acid vaccines may shorten the response time. Different DNA or RNA vaccines are currently under evaluation. The mRNA vaccine consists of an mRNA molecule of the virus that has been synthesized using laboratory techniques. After mRNA vaccine implementation, mRNA enters the cells, and spike protein is synthesized in the human body, so this type of vaccine saves months in the manufacturing process (41). mRNA vaccines are a good alternative to traditional vaccines with low cost, rapid production, and high potency. However, the RNA vaccine's safety and effectiveness in humans are unknown (43).

DNA vaccines are similar to mRNA vaccines in terms of safety and ease of production. However, they are poorly immunogenic, so they require multiple doses and the addition of an adjuvant (42).

According to the WHO report, 61 vaccine candidates are in clinical evaluation and 172 vaccine candidates in the pre-clinical assessment as of December 22, 2020 (13).

As a result, our current understanding of SARS-CoV-2 immunity is still limited. Further clarification of the immunopathogenesis of COVID-19 disease will guide us in both diagnosis and treatment. It will also shed light on novel drugs and vaccine studies. Therefore, extensive research is still necessary on the host immune response against SARS-CoV-2.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

REFERENCES

1. Su S, Wong G, Shi W, Liu J, Lai AC, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol.* 2016;24(6):490-502.
2. Tanrıverdi ES, Yakupoğulları Y, Otlu B. COVID-19 etkeninin özellikleri. Çiçek C, editör *Mikrobiyoloji ve COVID-19*. 1. Baskı Ankara: Türkiye Klinikleri; 2020:7-14.
3. İnal AS, Duman ZG, Kurtaran B. SARS-CoV-2 Mikrobiyoloji ve Patogenez. *AKTD.* 2020;29(Özel Sayı):11-23.
4. De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat. Rev. Microbiol.* 2016;14(8):523.
5. WHO. Middle East respiratory syndrome. Available at: <http://www.emro.who.int/health-topics/mers-cov/mers-outbreaks.html/> Accessed December 26, 2020.
6. JHU. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) Available at: <https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6> Accessed on December 29, 2020.
7. Çiçek C. *Epidemiyoloji.* 2020;Çiçek C, editör. *Mikrobiyoloji ve COVID-19*. 1.Baskı. Ankara: Türkiye Klinikleri; 2020:1-6.
8. WHO. WHO Coronavirus Disease (COVID-19) Dashboard. Available at: <https://covid19.who.int/> Accessed on December 20, 2020.
9. T.C. Sağlık Bakanlığı. Türkiye COVID-19 Hastalık Tablosu. Available at: <https://covid19.saglik.gov.tr/> Accessed on December 25, 2020.
10. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med* 2020; 383:2603-2615
11. WHO. Draft landscape and tracker of COVID-19 candidate vaccines. Available at: <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines/> Accessed on December 20, 2020.
12. NIH. Promising Interim Results from Clinical Trial of NIH-Moderna COVID-19 Vaccine. Available at: <https://www.nih.gov/news-events/news-releases/promising-interim-results-clinical-trial-nih-moderna-covid-19-vaccine/> Accessed on December 20, 2020.
13. WHO. Draft landscape and tracker of COVID-19 candidate vaccines. Available at: <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines/> Accessed on December 30, 2020.
14. Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. *Gene reports.* 2020:100682.
15. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020.
16. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh C-L, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science.* 2020;367(6483):1260-3.
17. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. *Nature.* 2020:1-6.

18. WHO. SARS-CoV-2 Variant – United Kingdom of Great Britain and Northern Ireland. Available at: <https://www.who.int/csr/don/21-december-2020-sars-cov2-variant-united-kingdom/en/> Accessed on December 26, 2020.
19. Chen Y, Liu Q, Guo D. Emerging coronaviruses: genome structure, replication, and pathogenesis. *J medical virol.* 2020;92(4):418-23.
20. Kurtaran B, Oto Ö. COVID-19 Pathogenesis. In: Taşova Y, Çelen MK, editors. *Coronavirus Disease 2019 (COVID-19): Turkey Perspective.* Ankara/Turkey: Hipokrat Yayıncılık; 2020. p. 21-7.
21. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. *Viruses.* 2020;12(4):372.
22. Lippi G, Lavie CJ, Henry BM, Sanchis-Gomar F. Do genetic polymorphisms in angiotensin converting enzyme 2 (ACE2) gene play a role in coronavirus disease 2019 (COVID-19)? *ClinChem Lab Med.* 2020; 58(9): 1415-22.
23. Alanagreh La, Alzoughoul F, Atoum M. The human coronavirus disease COVID-19: its origin, characteristics, and insights into potential drugs and its mechanisms. *Pathogens.* 2020;9(5):331.
24. Wang K, Chen W, Zhou Y-S, Lian J-Q, Zhang Z, Du P, et al. SARS-CoV-2 invades host cells via a novel route: CD147-spike protein. *BioRxiv.* 2020.
25. Ulrich H, Pillat MM. CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. *Stem Cell Rev and Rep.* 2020; 16:434–40
26. Wang K, Chen W, Zhang Z, Deng Y, Lian J-Q, Du P, et al. CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal Transduct Target Ther.*2020;5(1):1-10.
27. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmunity.* 2020:102433.
28. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.* 2020;8(4):420-2.
29. Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, et al. COVID-19: immunopathogenesis and Immunotherapeutics. *Signal Transduct Target Ther.* 2020;5(1):1-8.
30. Quan C, Li C, Ma H, Li Y, Zhang H. Immunopathogenesis of Coronavirus-Induced Acute Respiratory Distress Syndrome (ARDS): Potential Infection-Associated Hemophagocytic Lymphohistiocytosis. *Clin Microbiol Rev.* 2020;34(1).
31. Fidan I, Erganiş S. COVID-19 İmmünolojisi. Çiçek C, editör *Mikrobiyoloji ve COVID-19 1.Baskı* Ankara: Türkiye Klinikleri. 2020:74-82.
32. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol.* 2020;38(1):1-9.
33. Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J, et al. The landscape of lung bronchoalveolar immune cells in COVID-19 revealed by single-cell RNA sequencing. *MedRxiv.* 2020.
34. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, et al. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. *J. Exp. Med.* 2020;217(6).
35. Wang J, Li Q, Yin Y, Zhang Y, Cao Y, Lin X, et al. Excessive neutrophils and neutrophil extracellular traps in COVID-19. *Front. Immunol.* 2020;11:2063.
36. Bordallo B, Bellas M, Cortez AF, Vieira M, Pinheiro M. Severe COVID-19: what have we learned with the immunopathogenesis? *Adv. Rheumatol.* 2020;60(1):1-13.
37. Stephens DS, McElrath MJ. COVID-19 and the Path to Immunity. *Jama.* 2020;324(13):1279-81.
38. Lee WS, Wheatley AK, Kent SJ, DeKosky BJ. Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. *Nat. Microbiol.* 2020;5(10):1185-91.
39. Koirala A, Joo YJ, Khatami A, Chiu C, Britton PN. Vaccines for COVID-19: The current state of play. *Paediatr. Respir. Rev.* 2020;35:43-9.
40. Amanat F, Krammer F. SARS-CoV-2 vaccines: a status report. *Immunity.* 2020;52(4):583-9.
41. Kuşcu F. Current Status of COVID-19 Vaccine Studies. In: Taşova Y, Çelen MK, editors. *Coronavirus Disease Turkey Perspective.* Ankara/Turkey: Hipokrat Yayıncılık; 2020. p. 67-70.
42. Jeyanathan M, Afkhami S, Smail F, Miller MS, Lichty BD, Xing Z. Immunological considerations for COVID-19 vaccine strategies. *Nat. Rev. Immunol.* 2020;20(10):615-32.
43. Dong Y, Dai T, Wei Y, Zhang L, Zheng M, Zhou F. A systematic review of SARS-CoV-2 vaccine candidates. *Signal Transduct Target Ther.* 2020;5(1):1-14.