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Review Article

A Snapshot of Different Types of Under Research Vaccines Against COVID-19: A Review

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Abstract

SARS-CoV-2 as an emerging coronavirus, which first emerged in late 2019 in China causes a respiratory disease called "Coronavirus Disease 2019 (COVID-19)''. SARS-CoV-2 has since infected more than 26 million people worldwide and caused more than 864000 deaths as of September 04, 2020. The SARS-CoV-2 spike (S) protein consists of two subunits: S1 and S2, which plays a role in binding to cellular receptors and mediating the fusion process between the membranes of the virus and host cells. The S protein has an important role to induce neutralizing-antibody, as well as protective immunity, during SARS-CoV-2 infection. In this review, we focused on different types of the vaccine against COVID-19.

Keywords: SARS- 2, Vaccine, Novel Coronavirus, Coronavirus Disease 2019, SARS-CoV-2.

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Introduction

Nidovirales order is divided into three viral families including *Coronaviridae*, *Arteriviridae*, and *Roniviridae*. *Coronaviridae* as a large enveloped family is classified into four genera: alpha-coronavirus, beta-coronavirus, gamma-coronavirus, and delta-coronavirus (1). To date, six human coronaviruses (HCoVs) have been identified including HCoVs-229E, HCoVs-NL63, HCoVs-HKU-1, HCoVs-OC43, severe acute respiratory syndrome-CoV (SARS-CoV), and Middle East respiratory syndrome-CoV (MERS-CoV) that are members of alpha- and beta-coronaviruses (2). In December 2019, the novel coronavirus called SARS-CoV-2 was reported in Wuhan, China (3). Base on genetic analysis, SARS-CoV-2 belongs to beta-coronavirus genera. The symptoms of Coronavirus Disease 2019 (COVID-19), a disease caused by SARS-CoV-2, include fever, coughing, and shortness of breath; it can cause lung damage and acute respiratory distress syndrome and lead to lung disorders and death (4,5).

COVID-19 has spread rapidly around the world and posed a serious threat to public health. On 11 March 2020, the world health organization announced COVID-19 outbreak had turned into a pandemic (6,7). The origin of SARS-CoV-2 remains unknown yet; however, some studies have shown that animals such as bats, pangolins, snakes may be the potential hosts for this emerging virus (8). The genome analysis of SARS-CoV-2 reveals similarity to other beta-coronaviruses, which are found in bats. The genome sequence of SARS-CoV-2 is 96.2% similar to bat coronavirus (RaTG13), however, the SARS-CoV-2 genome shares 79.5% identity with SARS-CoV (5, 9). Such findings indicate that SARS-CoV-2 may actually has been derived from bats and transmitted to other non-human species over time and has recently been transferred to humans.

Currently, patients and carriers are the most important source of COVID-19. Prevalence and spreading speed of SARS-CoV-2 are higher than SARS-CoV therefore it has high transmission capacity in comparison with SARS-COV in the population (10). SARS-CoV-2 is transmitted via a variety of pathways including person to person (direct contact) through respiratory droplets, and indirect contact through fomites and aerosols (11). Some common symptoms of COVID-19 including fever of about 38°C, headache, cough, sore throat, fatigue, myalgia, and shortness of breath. Some patients with COVID19 have also reported gastrointestinal disorders such as diarrhea and vomiting (12). The mortality rate of SARS-CoV-2 depends on the severity of the disease. According to reports, the incubation period of the COVID-19 is one to 14 days and in most cases between 3 to 7 days (13). In general, all people are susceptible to SARS-CoV-2, although older people and people with underlying diseases are high-risk groups (14). SARS-CoV-2 can also infect children and infants, but symptoms in children are relatively mild which may be due to children's immune system functions (15).

SARS-CoV-2 genome

The genome of SARS-CoV-2 is approximately 30 kb (16). The 5′ end of the genome has an extended ORF1ab polyprotein, which produces non-structural proteins, although structural proteins are encoded in the 3′ end of the genome (17). As shown in (Figure 1) major structural proteins including the spike (S), membrane (M), envelope (E), and the nucleocapsid (N) protein (18).

SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) as the cellular receptor on the host cell for the binding and entry process, leading to severe respiratory disease (19).

Structure of the SARS-CoV-2 spike protein

SARS-COV-2 synthesizes spike glycoprotein as a single chain precursor that forms a trimer structure upon folding process, S glycoprotein belongs to class I viral fusion proteins such as hemagglutinin (HA) of influenza, paramyxovirus fusion (F) protein, ebolavirus glycoprotein 28 (GP), and glycoprotein 160 of HIV (20, 21). The molecular weight of each monomer of S glycoprotein is about 180 kDa and contains 1273 amino acids (22, 23). SARS-CoV-2 spike glycoprotein is a structural protein consisting of S1 and S2 subdomains. The S1 domain sequence is variable and responsible for binding to ACE2 as a cellular receptor, and the S2 domain with a conserved sequence has an important role in integrating the viral membrane into the cell membrane (24).

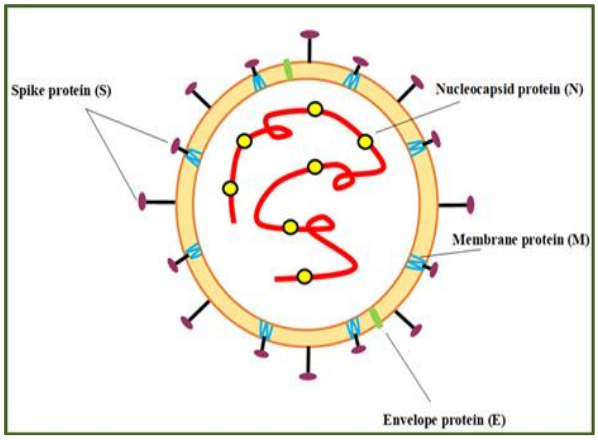

Figure 1. The overall structure Schematic of SARS-CoV-2.

SARS-CoV-2 and SARS-CoV utilize angiotensin-converting enzyme 2 (ACE2) to enter into the target cell where the virus replicates and spreads into other cells in the respiratory tract, SARS-CoV-2 binds to ACE2 through S glycoproteins (25). Amino acid 493 in the receptor-binding domain (RBD) of S protein has a vital role in the binding to ACE2 (3).

Computer analysis showed similar 3-D structures in the receptor-binding domain in S glycoprotein of both of SARS-CoV and SARS-CoV-2 (26), however, S glycoprotein of SARS-CoV-2 has a greater affinity to human ACE2 than SARS-CoV spike protein and it can play an effective role in transmitting the SARS-CoV-2 (3). There is a high degree of homology between S glycoproteins of SARS-CoV-2 and SARS-CoV, which in their S proteins display a sequence similarity of 75% (27). To bind the virus to the ACE2 receptor, an interaction between glutamine in the position of residue 394 in the SARS-CoV-2 spike protein and lysine 31 is necessary (28). Entry to the host cell is a vital step for virus replication, thus, ACE2 as a cellular receptor has an important role in both

SARS-CoV and SARS-CoV-2 replication cycle (29).

Recent studies showed that there is a mutation in the carboxyl-terminal region of the S1 domain of SARS-CoV-2 spike protein which can increase viral infectivity and transmission from person to person (30).

SARS-CoV-2 isolates which encode a D614G (S^{G614} to S^{D614}) mutation in S glycoprotein make a novel specific cleavage site for cellular protease which can affect infectivity, transmission, and severity of COVID-19 (31), therefore S glycoprotein can be a potential candidate for vaccine developing against SARS-CoV-2 worldwide (32).

In binding to the cellular receptor and membrane fusion, the essential roles of spike glycoprotein show that vaccines based on surface spike glycoprotein as a possible target will induce neutralizing antibodies to inhibit the process of virus binding and fusion (24). Spike glycoprotein has high immunogenicity among all structural proteins of SARS-CoV-2 that is responsible for inducing protective immunity against viral pathogenicity (33).

Vaccine design based on SARS-CoV-2 genome

Recently vaccine technology has significantly developed including the development of DNA and RNA vaccines, recombinant protein vaccines, vectored vaccines, and cell-culture-based vaccines (34).

To monitor the continuing COVID-19 pandemic triggered by the emergence of SARS-CoV-2, there is now an urgent need for a vaccine.

Spike glycoprotein of SARS-CoV-2 is a surface protein that facilitates entry of the virus into the host cells by binding to ACE2 as a cellular receptor, thus S glycoprotein can be an attractive vaccine target (35).

The viral life cycle is dependent on the interaction between S glycoprotein and ACE2, however, neutralizing antibodies target the spike glycoprotein and can lead to interference with SARS-CoV-2 binding to host cell, thus virus entry process and subsequent it's pathogenicity are inhibited (26).

Whole virus vaccines

The development of vaccines against COVID-19 can be facilitated by using experiences from efforts for designing vaccines against other emerging coronaviruses such as MERS and SARS (36). Different factors such as effectiveness, safety, the possibility of antibody-dependent enhancement (ADE), and other adverse effects before detection in MERS and SARS vaccines should be considered in experiments to design and develop an appropriate vaccine against COVID-19 (37).

According to the WHO, there are more than 130 candidate vaccines in five platforms for COVID-19 in clinical and preclinical evaluation (as of August 10, 2020) (Table 1) (38). Platforms of vaccines in the clinical evaluation are different including non-replicating viral vector, inactivated, DNA, and RNA. Due to its high immunogenicity and activation of toll-like receptors (TLRs) such as TLR3, TLR7/8, and TLR9, the inactivated or live-attenuated whole-virus vaccine strategy has been used for decades. Nonetheless, long-term monitoring is needed to assess its safety profile due to its viable nature. Many efforts are being made by some companies on the SARS-CoV-2 whole vaccine candidate due to the introduction of codon deoptimization technology for attenuating viruses (39).

Non-replicating viral vector

Viral vectors for both non-replicating and replicating forms are available including poxviruses and adenoviruses. Vectors designed primarily as replication-defective include adeno-associated virus, herpesvirus, and alphavirus. In fact, there are some advantages and disadvantages in Non-Replicating Viral Vectors like adenovirus that are used for a vaccine against SARS-CoV-2. They target mucosal inductive sites, infect dividing, non-dividing, and dendritic cells, and are physically and genetically stable without any integration. In addition, there are some disadvantages like; prior immunity to Ad5 and high doses needed to elicit immunity (40). Generally, pre-existing immunity to the Ad5 vector and increasing age could partially hamper the specific immune responses to vaccination; particularly the humoral immune responses are typically delayed. In this way, ChAdOx1-S, developed by the University of

Oxford in partnership with AstraZeneca, is the first vaccine candidate to reach phase III clinical trials (41).

A study has reported that a single dose of the vaccine can elicit a strong immune response in rhesus macaques (42). In addition, an experimental study in pigs showed that when given a booster dose, ChAdOx can elicit a higher antibody level, indicating that a double-dosing procedure can provide better protection in humans. ChAdOx1-S was well tolerated in humans, with no strong adverse effects seen in a sample of more than 320 vaccinated individuals (43).

Table 1. Candidate Vaccines in Clinical Evaluation

Platform	Type of candidate vaccine	The current stage of clinical evaluation	Developer
Non-Replicating Viral Vector	ChAdOx1-S[1]	Phases 1/2, 2b, 3	University of Oxford/Astra Zeneca
	Adenovirus Type 5 Vector	Phases 1, 2	CanSino BiologicalInc/ Beijing Institute of Biotechnology
	Adeno based	Phase 1	Gamaleya ResearchInstitute
Inactivated viral products	Inactivated+ alum	Phase 3	Sinovac
	Inactivated	Phases 1, 2	Wuhan Institute of Biological Products/Sinopharm
	Inactivated	Phases 1, 2	Beijing Institute of Biological Products/Sinopharm
	Inactivated	Phase 1	Institute of Medical Biology, Chinese Academy of Medical Sciences
DNA	DNA plasmid vaccine with electroporation	Phases 1, 2	Inovio Pharmaceuticals/International Vaccine Institute
	DNA plasmid vaccine	Phases 1, 2	Cadila Healthcare Limited
	DNA Vaccine (GX-19)	Phase 1	Genexine Consortium
RNA	LNP[2] encapsulated mRNA	Phases 1, 2	Moderna/NIAID
	3 LNP-mRNAs	Phases 1, 2	BioNTech/Fosun Pharma/Pfizer
Recombinant Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Phases 1, 2	Novavax

[1] Recombinant Chimpanzee Adenovirus Vector, [2] Lipid Nanoparticle.

Inactivated viral products

For the past 70 years, inactivated vaccines have been successfully used and are used commonly today.

In general, immunity caused by inactivated or subunit vaccines is more limited in length. A key factor in the pursuit of the latter approaches is safety. Concerns arise not only over the possibility of disease induction in vaccinated individuals, particularly those who are immune-compromised, but also over the spread of the vaccine virus in the population.

Regarding inactivated viral products in Table 1, Sinovac Biotech has demonstrated protection by PiCoVacc against SARS-CoV-2 in monkeys. Monkeys were immunized three times with two different doses (3 or 6 μg per dose) of PiCoVacc at days 0, 7, and 14 before the virus challenge in the third week.

One study showed that monkeys vaccinated against SARS-CoV-2 with PiCoVacc, produced SARS-CoV-2 neutralizing antibody titers similar to those of recovered patients. This study also showed that PiCoVacc is safe because no infection enhancement or immunopathological exacerbation was observed in vaccinated monkeys (44).

Recombinant protein subunit

The protection and immunogenicity study of the Novavax SARS-CoV-2–3Q-2P-FL immunogenic in mice and baboons revealed strong B- and T-cell responses to the vaccine without evidence of vaccine-associated enhanced respiratory disease

(VAERD) (45). This advanced protein subunit vaccine candidate currently being tested in humans appears stable, homogeneous, and locked in the antigenically preferred perfusion conformation (46).

World's first COVID-19 vaccine

The Sputnik V as a viral vector vaccine against COVOD-19 was developed by Gamaleya research institute. The same methods which were used for the Ebola vaccine have been also used for Sputnik V. Viral vectors are a relatively new technology for vaccine design. There have been several large clinical trials with viral vectors for Tuberculosis, Malaria, HIV, and Ebola, however, only one for Ebola has ever been approved for use in the general population (47). According to the Russian Ministry of Health, it is expected that the sputnik vaccine provides immunity from SARS-CoV-2, the virus that causes COVID-19, for up to two years. Sputnik V consists of two serotypes of human adenovirus and it is administered in two doses, each carrying an S-antigen of the SARS-CoV-2, which can enter into human cells and produce an immune response.

Conclusion

SARS-CoV-2 as a contagious agent quickly spreads all over the world. Among structural proteins of SARS-CoV-2, S protein has key roles in the binding and membrane fusion process, suggesting that S protein-based vaccines can activate antibodies to block virus infection. Therefore, S protein can be selected as an important target for vaccine and antiviral development. As mentioned above, S glycoprotein is the main component for the development of vaccines against SARS-CoV-2 infection. Full-length S protein can induce T-cell responses and neutralizing-antibodies, however, it might cause enhance infection or liver damage via harmful immune responses. The RBD of S glycoprotein induces neutralizing antibodies to block virus binding and membrane fusion process thus can inhibit the pathogenicity of SARS-CoV-2. Currently, vaccines that use viral DNA, mRNA, and micro genes are being studied in Phase I and Phase II clinical trials. Numerous ongoing clinical trials demonstrate that the science community is working actively to overcome this problem. As vaccines and specialized medications are not successful, prevention seems to be the best way to reduce the transmission of the virus.

Conflict of Interest

The authors declared that they have no conflict of interest.

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