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The Development of Vaccines against SARS-Cov-2 Virus. An Overview

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Abstract- The COVID-19 is a zoonotic disease and is caused by the SARS-CoV-2 virus. It is the type of coronavirus. The structural proteins of the virus include the spike (S) protein, membrane (M) protein, envelop protein (E), and nucleocapsid (N) protein. The replication of the virus utilizes all structural proteins. The infection of the host occurs due to the binding of the spike protein to the angiotensin-converting enzyme II (ACE II). It is a positive-sense single-stranded RNA virus belong to the family Coronavridae. The recent outbreak of this disease has caused a lethal pandemic. The previous knowledge of SARS-CoV has helped to develop a vaccine against SARS-CoV-2 also. The humoral and cell-mediated immune response is protective against this infection. The antibody response generated against the S protein, which is the most exposed protein of SARS-CoV, has been shown to protect from infection in mouse models. Multiple studies have shown that the antibodies generated against the N protein of SARS-CoV, are highly immunogenic and abundantly expressed protein during infections.

Keywords: SARS-CoV-2; COVID-19; vaccine; viral vector; coronavirus; live attenuated virus; protein sub-unit; virus-like particles (VLP).

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THEDEVELOPMENTOFVACCINESAGAINSTSARSCOV2VIRUSANDVERVIEW

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The Development of Vaccines against SARS-Cov-2 Virus. An Overview

Dr. Sujan Narayan Agrawal

Abstract- The COVID-19 is a zoonotic disease and is caused by the SARS-CoV-2 virus. It is the type of coronavirus. The structural proteins of the virus include the spike (S) protein, membrane (M) protein, envelop protein (E), and nucleocapsid (N) protein. The replication of the virus utilizes all structural proteins. The infection of the host occurs due to the binding of the spike protein to the angiotensin-converting enzyme II (ACE II). It is a positive-sense single-stranded RNA virus belong to the family Coronavridae. The recent outbreak of this disease has caused a lethal pandemic. The previous knowledge of SARS-CoV has helped to develop a vaccine against SARS-CoV-2 also. The humoral and cell-mediated immune response is protective against this infection. The antibody response generated against the S protein, which is the most exposed protein of SARS-CoV, has been shown to protect from infection in mouse models. Multiple studies have shown that the antibodies generated against the N protein of SARS-CoV, are highly immunogenic and abundantly expressed protein during infections. The T cell response provides long-term protection, maybe remain up to many years. Due to its possibility of long-term protection, it has attracted and provoked interest for the prospective vaccine against SARS-CoV-2. Among all SARS-CoV proteins, the T cell response against the structural proteins is the most immunogenic, as compare to the non-structural proteins. There are frenetic efforts to develop a vaccine against COVID-19, because of the pandemic situation. The various platforms are based on inactivated or live attenuated viruses, protein sub-unit, virus-like particles (VLP), viral vector (replicating and non-replicating) DNA, RNA, and nanoparticles, etc. Each candidate has some advantages and shortcomings. In this paper, an attempt is made to have an overview of the most promising vaccines for the infection by the SARS-CoV-2 virus.

Keywords: SARS-CoV-2; COVID-19; vaccine; viral vector; coronavirus; live attenuated virus; protein sub-unit; virus-like particles (VLP).

I. Introduction

The COVID-19 is a zoonotic disease and is caused by the SARS-CoV-2 virus. It is a type of coronavirus. The structural proteins of the virus include the spike (S) protein, membrane (M) protein, envelop protein (E), and nucleocapsid (N) protein. The replication of the virus utilizes all structural proteins. The infection of the host occurs due to the binding of the spike protein to the angiotensin-converting enzyme II (ACE II). Coronavirus is a positive-sense single-stranded RNA virus that belongs to the family Coronavridae. [1] These viruses mostly infect animals, including birds and mammals. In humans, they generally cause mild respiratory tract infection, just like the common cold. However, some recent coronavirus infections have resulted in lethal pandemics which include the SARS-CoV-2 virus. It belongs to the Beta coronavirus genus. [2] Its ~30 Kilobases genome size encodes for multiple structural and non-structural proteins just like other coronaviruses. Because of the recent discovery of the SARS-CoV-2 virus, the immunological information about this virus is limited. The preliminary studies have suggested that SARC-CoV-2 is quite similar to SARC-CoV based on full-length genome phylogenetic analysis. [3-4] The cell entry mechanism and human cell receptor usage are also similar. [5-6] This similarity in knowledge and researches help in understanding the immune responses and development of a vaccine against SARS-CoV-2. The previous studies also suggest a protective role of both humoral and cell-mediated immune responses. The antibody response generated against the S protein which is the most exposed protein of SARS-CoV has been shown to protect from infection in mouse models [7-8]

Multiple studies have shown that the antibodies generated against the N protein of SARS-CoV, are highly immunogenic and abundantly expressed protein during infections. [9-10] It was also found that antibody response was short-lived in the convalescent SARS-CoV patients. [11] The T cell response provides long-term protection, maybe remain up to many years. [12-13] Due to its possibility of long-term protection, it has attracted and provoked interest in the prospective vaccine against SARS-CoV-2. Among all SARS-CoV proteins, the T cell response against the structural proteins is the most immunogenic, as compare to the non-structural proteins [14] T cell response against the S and N proteins has been reported to be the most dominant and long-lasting, and both are structural proteins. [15]

There are frenetic efforts to develop a vaccine against COVID-19, because of the pandemic situation. The various platforms are based on inactivated or live attenuated viruses, protein sub-unit, virus-like particles (VLP), viral vector (replicating and non-replicating) DNA, RNA, and nanoparticles, etc. Each candidate has some advantages and shortcomings. [16] The immunogenicity is enhanced by adding adjuvants. [17] The immune-

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informatics approach is also used for the epitope identification of vaccine candidates. They are used to identify the significant cytotoxic T cells and B-cells epitopes found in the viral proteins. [18-19]

II. Nucleic acid Vaccine

The nucleic acid vaccines use genetic material from the disease-causing virus or a pathogen to stimulate an immune response against it. Depending upon the type of vaccine, the genetic material could be DNA or RNA. In the case of COVID-19 this usually the viral spike protein. Once this genetic material goes into human cells, it uses our cells to make the antigen that will trigger an immune response. There are many advantages of nucleic acid vaccines, they are easy to make, and are cheap. The antigen is produced inside our cells so the immune response is strong. It has got certain disadvantages too, however, so far, no DNA or RNA vaccine has been licensed for human use. The RNA vaccines are needed to be kept at an ultra-cold temperature (i.e., -70O C or lower) and it can be a real challenge for the countries that don't have the specialized cold storages. This is the main hurdle particularly in the low- and middle-income countries.

The DNA vaccine: These are the most revolutionary approach to the vaccination program. These DNA vaccines encode for the antigen and an adjuvant which induces the adaptive immune response. The transfected cell expresses the transgene, and it provides a steady supply of the transgene-specific protein. This phenomenon is quite similar to the live virus. They also stimulate effective humoral as well as cell-mediated immune response. [20] The mRNA vaccines: They are an emerging, non-infectious and non-integrating platform of vaccine development. They have no potential risk of insertional mutagenesis. This platform has the potential for a rapid vaccine development program due to its flexibility. It can mimic the antigen structure and the expression as seen with the natural infection. [21] The example of the mRNA vaccine is Pfizer BioNtech and Moderna vaccines.

The Moderna vaccine is composed of synthetic mRNA encapsulated in a lipid nanoparticle (LPN) which encodes for the full-length, pre-fusion stabilized spike protein (S) of the SARS-CoV-2 virus. It does not contain inactivated pathogen or sub-units of the live pathogen, so it is relatively safe.[22] The vaccine has got fast-track approval from FDA to conduct the phase II trial.[23] Another mRNA vaccine is by BioNtech/Pfizer. It is a codon-optimized mRNA vaccine and it encodes for the trimerized SARS-CoV-2 RBD. It has good immunogenicity. The mRNA is encapsulated in an ionizable lipid nanoparticle. This ensures its efficient delivery. The post-vaccination reactions are local and transient, and there are no systemic events. [24]

III. The Whole Virus Vaccines

One of the common ways to make a vaccine is to use inactivated or killed virus or microbe. They are inactivated by chemicals, heat, or radiation. The technology for making such vaccines has proven technology and know-how. Moreover, they can be manufactured on a reasonable scale. The drawback is it requires special laboratory facilities to grow the virus or bacterium safely. It has a relatively long production time, and it requires two or more doses. Examples of this approach are flu and polio vaccines. It can also be given to people with a compromised immune system. Yet another approach is to use a living but weakened version of the virus (live attenuated). The technology used to manufacture the vaccine are similar to the inactivated vaccine. However, these vaccines may not be suitable for people with the compromised immune system. The measles, mumps, and rubella (MMR) vaccine and chickenpox and shingle vaccines are examples of this type of vaccine. [25]

The advantages of live attenuated vaccines are: they have well-established technology. They evoke a strong immune response, which involves B cells and T cells. They are simple to manufacture. The disadvantage is that they are unsuitable for the compromised immune system. They are relatively heat-labile so, they require cold storage facilities. The live attenuated vaccine developed by the University of Hong Kong (DelNS1-Sars-CoV2-RBD) is influenza-based. There is the deletion of the NS1 gene. It is re-organized to express the RBD domain of SARS-CoV-2 spike protein on its surface. It is cultivated in the chick embryo and /or Madin Darby Canine Kidney Cells (MDCK) cells. It is potentially more immunogenic than the wild type of influenza virus. It can be administered as a nasal spray. [26]

IV. Protein Sub-unit Vaccines

A subunit vaccine is based on the synthetic peptide or recombinant antigenic protein. They are necessary to produce the immune response. [27] The existing hepatitis B vaccine is an example of a subunit vaccine. These subunit vaccines exhibit low immunogenicity and require an adjuvant to potentiate the vaccine-induced response. It has been found that the S protein of the SARS-CoV-2 is the most suitable antigen to induce the antibodies against the pathogens. The virus enters the cell via endocytosis, for this, it utilizes the S-protein mediated binding to the hACE2 receptors. The S-protein and its antigenic fragments are the prime targets for making the subunit vaccine. [28] The NVX-CoV2373 (Novavax, inc/emergent BioSolutions) is a nano-particle-based vaccine. It is based on the recombinant expression of the stable pre-fusion, coronavirus S-protein. [29-30] The subunit vaccines are also called acellular vaccines because they

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contain a purified piece of protein that can evoke an immune response. These fragments are incapable of causing the disease so they are considered very safe options. They are of many types: proteins from viral or bacterial pathogens, or polysaccharide vaccines containing chains of sugar molecules, or conjugate subunit vaccines, they bind a polysaccharide chain to a carrier protein to try and boost the immune response. At present, only protein sub-unit vaccines are being developed against the coronavirus. The subunit vaccines are already in use. The hepatitis B and pertussis vaccines are examples of protein subunits. The pneumococcal vaccine and MenACWY vaccine are polysaccharide vaccines. These subunit vaccines produce a strong and effective immune response. The risk of side effects is minimal. Such vaccines are relatively cheap and easy to manufacture. They are also more stable than those vaccines containing viruses or bacteria. These vaccines contain the adjuvants to boost the immune system and also, they require a booster dose.

V. Viral Vector Vaccines

The vaccines based on viral vectors are highly promising. They are very specific in delivering the gene to the targeted cell. The gene transduction is very efficient and induces a good immune response. [30] They offer a long-term antigenic protein expression. It also triggers and prime the cytotoxic T cells (CTL) and thus ultimately leads to the elimination of the infected cells. [31] The concept of the viral vector was introduced in 1972 with recombinant DNA from the SV40 virus.[32] The vaccinia virus was used subsequently as a transient gene expression vector in 1982. [33]

The ad5-nCoV vaccine developed by the CanSino Biologics inc/Beijing Institute of Biotechnology is an example of a viral vector vaccine. It is a recombinant, replication-defective, adenovirus type-5 vector (Ad5) expressing the recombinant spike protein of SARS-CoV-2. It is developed by the cloning optimized full-length gene of the S protein. The cloning is done with the plasminogen activator signal peptide gene in the Ad5 vector. [34] *Coroflu* developed by Bharat Biotech is a vaccine given by the intra-nasal route thus mimicking the natural route of the viral infection. M2SR is a version of the influenza virus. It is modified by the insertion of the SARS-CoV-2 gene sequence of the spike protein. This vaccine expresses the hemagglutinin protein of the influenza virus, and thus it induces the immune response against both the viruses. This influenza virus is a self-limiting virus and does not undergo replication since it is lacking the M2 gene. The intra-nasal route activates several modes of the immune system and thus it has higher immunogenicity as compared to the intramuscular injection. [35] The vaccine LV-SMENP-DC is developed by engineering the dendritic cells (DC) with the lentiviral vector expressing the conserved domain of the SARS-CoV-2 structural proteins and the protease using the SMENP minigene. The vaccine is given subcutaneously. It activates the cytotoxic cells and generates the immune response. [36] Viral vectors are used to develop a vaccine against COVID-19. Adenovirus-based vectors are the most preferred approach. It elicits robust antibody response and offers protection against SARS-CoV-2. The classical route of delivery of vaccine is intramuscular but intranasal spray has also been promising. It has also been demonstrated that the prime-boost strategies provide superior immunity and protection.

VI. Conclusion

The duration of the clinical trials is the greatest hurdle for the development of any new vaccine. As per FDA, a vaccine candidate has to pass through at least three phases of placebo-controlled trials for validation of its safety and efficacy, and it may take years to gather. The safety trials are to be conducted for the children, pregnant women, and immune-compromised patients before the extension of vaccination for this group. [37] The viral genome is in a process of constant change and mutation. The mutations vary according to the environment, population, population density, and geographical area. The scientist identified approximately 198 mutations of the virus inside the human host. These mutations may lead to the formation of different subtypes and thus allow the virus to escape the immune system, even after vaccination. [38] There is a large number of vaccine candidates for the COVID-19 disease and are based on various platforms. The various stages of vaccine development and quite a lengthy and laborious process. This includes the clinical and preclinical trials. Due to this pandemic scientific community is using the unconventional approach to accelerate the process of vaccine development and of course without compromising with the safety and quality. As per the WHO: “vaccine must provide a highly favourable benefit-risk contour; with high efficacy, only mild or transient adverse effects and no serious ailments.” It must be suitable for all ages, pregnant, and lactating mothers and should provide a rapid onset of protection. It should also provide immunity at least for one year with a single dose.

In India, six biotech companies are venturing in developing vaccines against coronavirus. They are Serum Institute of India, ZydusCadila, Biological Evans, Indian Immunologicals, Bharat Biotech, and Mynvax. They are working on DNA vaccines, live attenuated recombinant measles vaccines, inactivated viral vaccines, subunit vaccine, and vaccines developed by Condon-optimization, [39] Currently there are more than 100 candidates SARS-CoV-2 vaccines under development. The World Health Organization (WHO)

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regularly publishes an updated list of vaccines in development. All these can be accessed at https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines). The universal priority is to develop a safe and effective COVID-19 vaccine that can induce an appropriate immune response, to combat this pandemic.

Ethical issues: None.

Financial Implications: None.

Competing Interest: None

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