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***Corresponding Author**
Savaira Jabbar

E-mail
savairajabbar1234@gmail.com

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Immunological considerations and vaccines against COVID-19

Savaira Jabbar*, Abrar Younas

Department of Microbiology and Molecular Genetics, Faculty of Life Sciences, University of Okara, Punjab 56300, Pakistan

Abstract

The outbreak COVID-19 is considered as a revolution in history of biological science. SARS-CoV-2 is a main cause of COVID-19 having resemblance with MERS-CoV and SARS-CoV. The response of host to the infection of SARS-CoV is multiform and strong. Initially, an effective host defense in the lung is affiliated with disease resolution and mild symptoms. The escaping of virus from immune response can lead to damage the alveoli, systematic inflammation, and ineffective lung repair mechanism with associated organ dysfunction. The immunological responses are necessary to fight with the virus and an effective and a safe vaccine is needed to overcome the pandemic. The development of vaccine is progressing fast, billions of dollars committed with more than 200 candidates before even knowing whether a vaccine candidate will succeed.

Introduction

COVID-19 is a contagious disease that affects the respiratory system and caused by SARS-CoV-2, a new coronavirus. Similar to SARS, fulminant pneumonia has been developed. SARS-CoV-2 transmits by droplets from mouth and nose. Notably, the active disease is not developed by 80% of people who are infected or exposed. The mild symptoms of seasonal flu have been observed by the people however they get over illness without major treatment. Despite of this, its approximate rate of incidence is 20-60% as compared to 8% for flu. The conclusion of basic knowledge is that the period of hospitalization is twice for patients developed severe symptoms. In late 2019, it was emerged in a province of China, Hubei and spread globally through transmission from one individual to other [1]. After SARS-CoV and MERS-CoV, the third member of the pathogenic coronavirus is SARS-CoV-2 and severe pathology was observed by this virus among others and mild clinical symptoms were shown in humans including flu [2] .

Various immunological considerations and effects for COVID-19 and different types of vaccines were summarized in this article. Structurally, coronavirus is an enveloped pleomorphic virus with a group of projections made up of S protein. The virus possesses a positive sense ssRNA genome complexes with a protein called N protein and form a helical nucleocapsid. The genome of SAR-CoV-2 is polyadnylated and also capped [3] [4] 79% similarity has been revealed by the genetic analyses of SARS-CoV and SARS-CoV-2 with substitutions of 380 amino acids mainly compressed within the genes known as NSP (Non-structural protein) genes. In the immune-dominant S protein, there are 27 amino acid substitutions while 61 and 102 amino acid substitutions are present in NSP2 and NSP3 respectively. Whereas, some accessory proteins, E protein, NSP13, NSP7 don not have any substitutions of amino acids [5] The transcription of SARS-CoV-2 genome is occurred in at least 10 Open Reading Frames (ORFs). The translation of a polyprotein is occurred by ORF1ab and polyprotein is processed into 16 non-structural proteins (NSPs) [6] .

There are four structural proteins contained by SARS-CoV-2 named as membrane (M), envelop (E), nucleocapsid (N) and spike (S). These proteins are encoded by 3' end of virus genome. The important role of viral attachment, fusion and entry into host cell is played by large multifunctional transmembrane S glycoprotein [7]. Human angiotensin-converting enzyme 2 (hACE2) receptors are used by SARS-CoV-2 to block the target cell through the S protein (spike glycoprotein) [8]. Viroporins are formed by E protein involved in a numerous functions in the replication cycle of virus including pathogenesis [4]. The main organizer for the assembly of CoV is M protein and is responsible for assembly and morphogenesis of SARS-CoV-2 by joining with structural proteins [9]. These proteins have significance in the development of vaccine against COVID-19.

Responses mediated by innate immune system

Current studies propose that the immune responses for SARS-CoV-2 are same to the responses for MERS-CoV and SARS-CoV in a few manners [10] [11] [12]. Similar to MERS-CoV and SARS-CoV, SARS-COV-2 abolishes the initiation of innate immune system consisting of dendritic cells [13], [14] and inhibits the responses of antiviral type 1, type 2 and type 3 interferons [15]. SARS-CoV-2 has the ability of innate immunity may account for prolonged period of incubation of about 2-12 days for COVID-19 as compared to the incubation period of about 1-4 days for influenza. Thus, in the first step of infection, replication of SARS-CoV-2 suppressed and shows inflammatory responses that are dysregulated especially in critical cases of COVID-19 [16]. These critical cases are diagnosed by greater numbers of neutrophils and monocytes in blood that are inflammatory [17], [18]; CD14+, CD16+ macrophages derived by monocytes in the air way and amplified systematic levels of inflammatory chemokines and cytokines [19]. The immunopathology consisting of acute respiratory distress syndrome, great viral burden and dysregulation, possibly lethal, inflammatory responses are the results of failure to attain prior control to SARS-CoV-2. Because of this, elders and those with co-morbities may be markedly disposed to COVID-19 having immunosenescence and their ability to post the inflammatory responses that are amplified [20].

Antibody responses

In most infected individuals, IgG and IgM antibodies in respond to SARS-CoV-2 are recognized within 1-2 weeks [21]. Despite of this, the affinity between T-Cells that are antigen specific, neutralizing

antibodies, disease excessive sternness and clinical results left to be understood. The elevated levels of antibodies that are neutralizing have been studied in recovered individuals [22]. This has relationship with responses mediated by T-cell especially CD4+ T-cells. These are suggested to purpose some worthy aspects in studies with convalescent plasma [23]. Latest studies demonstrate that the importance of responses by neutralizing antibody is positively associated with the severity of disease [24]. Thus, in most of the people who are infected with SARS-CoV-2, the antibody responses decrease within week that is a property of responses by antibody to other coronaviruses causing common cold [8].

S protein is the main target of neutralizing antibodies. This protein is made up of S1 and S2 domains. S contains RBD and is a distal membrane. These RBD attach to a cellular receptor known as ACE2. S2 is a proximal membrane and is responsible for the fusion of membrane [25]. The S proteins of SARS-CoV-2 and SARS-CoV have 88% similarity and both attach to ACE2 [26]. The interaction between RBD and ACE2 is blocked by antibodies that bind to S1, whereas the conformational change can be constrained and membrane fusion can be blocked by those that attach to other region of S1 and S2 respectively [27] [28].

The high concentration of antibodies is also developed against abundant protein of virus nucleoprotein (N) during responses by natural immune system to SARS-CoV-2 [29] [30]. Although, antibodies against N are contrarily to defuse the virus, they have been declared to grant stability against a mouse's coronavirus named as mouse hepatitis virus. Conspicuously, these antibodies were IgG2a, demonstrating that rather than direct virus neutralization they may protect through Fc mediated effector functions [31] [32]. Many evidences have proposed that IgA responses against S protein apex before the IgM responses are much articulated, forms IgA a potentially adorable goal for antibody-based analytical valuations [33], [34]. The mechanical basis of inauguration of S protein specific IgA is vague till.

The persistence of the responses by antibodies to SARS-CoV-2 is still not clear. Between 1 year and 2 year after infection, there is substantial decrease of neutralizing antibody concentration in patients [35], [36]. This is persistent with traditional studies presenting a considerably swift decrease of antibodies against the seasonal 229E coronavirus [37]. As there are no immune corresponds yet known for the protection against infection, hence it is not clear that how many neutralizing antibodies are enough to deal with the disease. These corresponds will be necessary for the development effective vaccines.

Immunity mediated by T-cell

The need of both immunities mediated by T- cell and antibody is suggested by emerging documentation for adequate protection against COVID-19. It was evidenced that the T- helper cell is responsible for the activation of cytotoxic cell for optimal antibody responses [38]. Moreover, if protection mediated by neutralizing antibody is inadequate, cytotoxic cells are necessary for removal of virus. 100% S protein specific T-helper cells and 70% S protein specific cytotoxic cells had been founded in the circulation among persons who had recovered from COVID-19 [37]. In host defense against SARS-CoV, a protective role T cells is shown by preclinical studies [39].

The incubation period of about 2-12 days for SARS-CoV-2 is not just associated to the innate immune suppression mediated by virus but it is also associated to the delayed initiation of T cells, especially cytotoxic cells. Compared with severe cases, people who have recovered from milder infection of COVID-19 have more number of memory cytotoxic cells in the respiratory system. Strong lung tissue resident memory cell responses are induced by Respiratory mucosal vaccination [40] [41], [42]. Experimentally, the lung tissue resident memory cells provoked by respiratory mucosal immunization provided strong security against infection of SARS-CoV [43]. T-helper cells are induced through vaccination for protection and mediation. Less critical cases of SARS were co-related to activate the induction of a T-helper 1 cell response [44], however T-helper 2 cell responses have been related with severe lung disease by following infectious hosts immunized with neutralized SARS-CoV viral vaccines [45] [46] [47].

Pre-existing immunity

The T helper cells in 35% fit individuals not exposed and recognize S protein of SARS-CoV-2 but T-helper cells in 40-60% of unexposed people are responsive to proteins other than S protein of SARS-CoV-2 [48]. This shows that there is cross-reactivity between T-helper cells definite for human common cold coronaviruses and for SARS-CoV-2, animal beta coronaviruses and SARS-CoV [49], [50] [50].

There are four types of human coronaviruses namely HKU1, OC43, NL63 and 229E. These viruses account for ~15% of common colds. One of these viruses may infect the individuals for every 2-3 years on average and thus there might be extent of cross-reactive immunity which is pre-existing against antigens of SARS-CoV-2.

Protein subunit vaccines

The vaccines based on recombinant antigenic proteins or synthetic peptides that are important for activating permanent therapeutic and protective immune response [51]. Basically, subunit vaccines induce T-helper cells and responses mediated by antibody. Consequently, many of the subunit vaccines have full length S protein of SARS-CoV-2 or part of it with the purpose of prompting neutralizing antibodies. This is as same as many of the vaccines against MERS-CoV and SARS-CoV and had different efficacy levels [52], [53], [54]. These vaccines could be prepared to focus the immune response for neutralizing epitopes and then propagation of antibodies that are non-neutralizing and can improve the antibody dependent development of disease [55].
In subunit vaccines, recombinant S proteins could have an incorrect epitope conformation. Alone peptides or proteins are immunogenic to some extent and usually not an adjuvant simply but also control and weakens the activators of responses mediated by cytotoxic cell. Moreover, this is inappropriate platform for respiratory mucosal vaccination [56]. However, subunit vaccines show low immunogenicity and needs extra platform of an adjuvant to increase the biological half-life of the antigenic material and can improve the responses by immunomodulatory cytokine. Therefore, an adjuvant's addition assists in incapacitating the deficiency of the protein subunit vaccines [47]. S protein of is the most acceptable antigen for the activation of neutralizing antibodies. S1 subunit comprises of RBM (RNA binding motif), RBD (Receptor binding domain) and NTD (N-terminal domain) domains whereas S2 subunit consists of HR, FP 1 and 2 [17]. The virus goes into the cell through endocytosis by employing the S protein interposed binding with the receptor known as hACE2 receptor. Consequently, S protein and its antigenic portions are the first objects for the organization of subunit vaccine. S glycoprotein is a high powered protein, carrying two conformational states; pre-fusion and post-fusion. Hence, the antigen must retain its interaction of surface and lineament of the primary pre-fusion S protein to conserve the epitopes for initiating admirable value of antibody responses [57]. Furthermore, in order to target a masked RBM as an antigen will upsurge the neutralizing antibody response and elevate the overall efficiency of the vaccines.

NVX-CoV2373

NVX-CoV2373 is an immunogenic nano-particle based developed by Novavax. This vaccine depends upon the recombinant expression of coronavirus S protein's stable pre-fusion [58]. The protein was strongly shown in a Baculovirus system [59]. The company aims to consume the Matrix-M adjuvant for the rise in immune response against viral S protein by inducing the much levels of neutralizing antibodies. The hACE2 receptor binding domain was blocked by high level of anti-S protein antibodies and can introduce SARS-CoV-2 wild type virus-neutralizing antibodies in animal models.
It was also applied in 131 healthy persons between 18 and 59 years old without Matrix-M adjuvant. Its immunization requires two repeated doses of IM injection.

Triple antigen vaccine

This vaccine is being manufactured by Premas Biotech, India. It is a prototype with multi antigenic VLP vaccine in which the membrane, envelop protein and recombinant spike have been joined in an engineered *Saccharomyces cerevisiae* expression platform (D-Crypt ^{TM}). Then, proteins get together as the VLP. Simultaneously the biophysical depiction of the VLP was provisioned by TEM and allied analytical data. Moreover, it is considered to be safe and not burdensome to produce on a large scale in a money-making way [60].

PittCo Vacc

This vaccine was being designed by University of Pittsburgh. It is a Micro-Needle Array based recombinant vaccine that involves the control of recombinant immunogens of rSARS-CoV-2 S1 and rSARS-CoV-2 S1fRS09. A significant enhancement in the antigen specific antibodies with a statistical connotation was examined in the preclinical trials at the termination of two weeks in the mice models. Moreover, the immunogenicity of vaccine was observed correctly even after the sterilization by

using gamma radiation. The statistically specified number of antibodies at the premier phase and also improving presentably help the feasibility of the MNA-SARS-CoV-2 vaccine [61].

Viral Vector-based vaccines

In these vaccines, the antigen is cloned in a viral vector which does not have the ability to reproduce. Mostly used viral vectors are adenovirus, lentivirus and adeno-associated virus (AAV). The viral vector inhibits the infection and can generate tougher cellular immune responses than the recombinant protein vaccine. During the previous SARS-CoV, vaccine candidate was designed using AAV vector [62]. A viral vector-based vaccine is reassuring with prophylactic solutions against SARS-CoV-2. These vaccines are very much specific in transporting the genes to the target cells, highly proficient in the gene transportation and perfectly induce the immune response [63]. Long lasting and high level of antigenic protein manifestation are offered by them. They have a high potential for prophylactic use as these vaccines activate and initiate cytotoxic T cells which finally directs to the suppression of cells infected by virus.

Ad5-nCoV

It is a replicated, recombinant and imperfect adenovirus type-5 vector showing the recombinant S protein being developed by CanSino Biologics Inc. Beijing Institute of Biotechnology. It was formulated by cloning a modified full-length gene of the S protein with plasminogen activator signal peptide gene in the Ad5 vector consists of E3 and E1 genes. This vaccine was prepared by using the Admax system from the Microbix Biosystem [64]. The phase I clinical trials had installed a positive antibody response. A fourfold enhancement in the RBD and S protein specific neutralizing antibodies was recorded within 14 days of immunization and proved at day 28, post vaccination. Published data shows that the vaccine is not effective as high doses elicit neutralizing antibodies in approximately 50-60% of vaccines ad and negatively linked to the pre-existing anti-vector immunity in persons above 55 years old.

LV-SMENP-DC

This vaccine is constructed by Shenzhen Geno-Immune Medical Institute by engineering the dendritic cells with the lentiviral vector showing the sustained domains of the proteins using minigenes SMENP. The subcutaneous inoculation of the vaccine exhibits antigen on APCs that finally activate the cytotoxic T cells and provoke the immune response [65].

ChAdOx1

This vaccine was formulated by University of Oxford, AstraZeneca and clinical trial was in UK, Brazil, USA and South Africa. Codon optimized S glycoprotein was used to develop this vaccine and produced 5' end with a tissue plasminogen activator leader sequence. Shuttle plasmid was used to propagate the tPA leader and sequence of coding for amino acids (2-1273). For the encoding of highly immediate genes of human cytomegalovirus, this shuttle plasmid was used. This was done by polyadnylation signal from bovine growth hormone and tetracycline operator sites. The viral genome is produced by inserting inducing the S gene into E1 locus of ChAdOx1 adenovirus. Published data indicates that the vaccine does not prevent transmission in NHPs but is useful to prevent pneumonia [66].

mRNA vaccines

The mRNA vaccine is an advanced group of vaccines in which all elements can be generated via chemical synthesis. Since the antigen expression from mRNA is a short term mechanism, a risk of the host DNA assimilation is imperceptible. An abrogation of using living components is a beneficial to a quality control perspective and grants swift item exchanging in developing facilities. That is why different proteins contradict just in the sequence of RNA molecules that can be easily altered in a process of solid phase synthesis [67].
The molecules of mRNA occur in nature have small apparent transfection ability. Therefore, the lipid nano-particles are probably used to induce the mRNA molecules for the purposes of transfection [68]. A characteristic LNP formulation composed of a lipid condensing with RNA to make a complex with a molecule of mRNA, helper lipids for providing the structural rigidity and lipidized polymer coating for the amendment in the surface characteristics of particles [69]. Once phagocytosed by cell, LNPs undergoes to an endosome of low pH environment. The lipid condensing with RNA can rupture the endosome and permit the molecules of

mRNA released in cytosol. Hence, key component of this platform is RNA condensing lipid [70].

BNT162b1

It is a codon-optimized mRNA vaccine which encrypts for trimerized SARS-CoV-2 RBD, an important target of virus is nAb. Vaccine induces an enhanced immunogenicity. This enhancement is the result of the accumulation of domain derived by T4 fibritin fold on the trimerization to RBD antigen. The efficient delivery of mRNA is ensured by its property being encapsulated in 80nm ionizable cationic lipid nano-particles. [71].

mRNA-1273

This vaccine consists of synthetic mRNA which is wrapped in lipid nano-particles. This LNP encodes for the pre-fusion, full-length stabilized S protein. It has an ability to elicit an antiviral response specified by S protein. . This vaccine is considered to be safe as it induces 100% of T helper cells responses and 100% of neutralizing antibodies responses [72].

Other vaccines

Many of the other vaccines have been developed or under development including DNA vaccines, trained immunity-based vaccines and bacterial vector-based vaccines. British and American Tobacco Company (BAT), CanSino Biologics, University of Oxford, Tianjin University and many others in all over the world are struggling to develop an effective vaccine.

Conclusion

The number of breeding of model animals do not meet the demands of researchers around the globe. The major problem is that the developed vaccines are testing by laboratory animal models. There is too much difference between ACE2 receptors of humans and mice. Furthermore, the genome of SARS-CoV-2 is vulnerable to mutations and as it spread from one population to other can undergo the antigenic drift and antigenic shift. All these reasons are responsible to make a vaccine ineffective.

While considering the immunological aspects, the infection caused by virus SARS-CoV-2 is under detection and body is already being fighting against the disease. But the severity of disease and pressure exerted by this pandemic moved the scientists to work for the progress of safe and effective vaccine. In this regard, many of the vaccines have been designed the immunogenicity and thus overcome the infection. These vaccines undergo clinical trials and providing either a candidate is effective or not. But main reason for the limitation of a vaccine is a mutation in the genome of virus SARS-CoV-2. Thus the conformational proteins of virus are of main concern for immunogenicity and development of vaccines.

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Conflict of interest

The authors declare no conflict of interest.

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