Review Article

SARS-CoV-2 Immunity: Review of Immune Response to Infection and Vaccination

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Abstract

After the last flu pandemic in 1918, the world has not faced a similar pandemic until now. However, it has been possible to identify the causative agent as well as its structure and function. The SARS-CoV-2 virus attacks the respiratory system, and the viral components like the spike protein and nucleocapsid protein produce an immune response in the host for viral elimination. The antigen can be recognized by or is presented to T cells. This results in neutralizing antibody production, cytokine secretion, and cytolysis. Although most infected individuals only suffer mild or moderate disease, some develop cytokine storms due to excess formation of cytokines resulting in ARDS, multiorgan failure, and DIC. The virus has mechanisms in place that can aid its escape from the host's immune response. Vaccine development has been underway around the globe to produce effective vaccines to limit morbidity and mortality from infection. Vaccines like mRNA vaccines encode the spike protein of coronavirus, and research has shown that antibodies developing from the vaccine were less affected by mutation in the spike protein of the virus than that developed from infection. The mRNA vaccine has modified nucleotide that limits the excessive formation of Interferons. Although various hurdles to overcome to vaccinate the world population effectively, vaccination may be essential to control the pandemic and a return to normalcy. This review highlights the current knowledge on the structure of the virus and the immune response triggered by the virus in infected individuals. It also reviews the currently available vaccines with their formulation, mechanism of immune response elicited.

Keywords: Pandemic, SARS-CoV-2, infection, Immune response, T helper cells, Neutralizing antibodies, Vaccine

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Introduction

Since the identification of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in December 2019, over 4 million of the world's population have succumbed to death after being infected with the virus by July of 2021[1-3]. There are seven coronaviruses known to cause infection in humans: the 4 seasonal Coronaviruses causing self-limiting upper respiratory tract infections and 3 Coronaviruses with high pathogenicity (SARS-CoV-1, MERS [Middle East respiratory syndrome], and SARS-CoV-2). These highly pathogenic Coronaviruses, SARS-CoV-1, MERS, and SARS-CoV-2, have emerged in 2003, 2012, and 2019 respectively[4,5]. There is limited knowledge regarding the immunity to all Corona viruses[4]. Individuals who suffer from seasonal Coronaviruses tend to develop immunity for about one year, while the quantity of antibodies acquired from infection with SARS-CoV-1 and MERS significantly decreases 2-3 years following the onset of symptom individuals susceptible to reinfection [6-8]. The understanding of the immunity against SARS-CoV-2 has been developing through sero surveillance studies conducted during the pandemic and evaluating B- and T-cell responses to SARS-CoV-2 among convalescent subjects with varying degrees of severity of disease[9].

The diminution of the pandemic of COVID-19 is dependent on the world population acquiring immunity through infection with or by receiving the

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vaccination against this virus. However, it has been observed that human beings are susceptible to repeated infection with 'common cold' coronaviruses[10]. One of the reasons for such reinfection is that these coronaviruses tend to alter their structure to escape the immunity given by antibodies developed from previous infection [11]. Similarly, SARS-CoV-2 has been evolving and generating new lineages with decreased neutralization by antibodies produced from prior infection and vaccination[12-16]. Although the human immune system offers considerable protection against infection and severe forms of the disease caused by the new variants[17,18], viral evolution will eventually overcome this protection of immunity against reinfection[19].

Effective vaccines may be the answer to controlling the pandemic. Initiatives have therefore been underway for the rapid development of vaccines. The licensed vaccines at present for SARS-CoV-2 have been based on the SARS-CoV-1 and MERS experience. However, the developed vaccines for SARS-CoV-1 and MERS did not progress further than phase 1 of clinical trials[20]. At present, there are more than 270 COVID-19 vaccine development in progress that includes more than 90 in clinical trial[21-23] and include Nucleic acid vaccines (RNA and DNA) [24-27], whole-cell inactivated virus[28,29], human and simian replication-deficient and replication-competent adenoviral-vectored vaccines[30,31] and whole-cell inactivated vaccines CoronaVac (Sinovac Biotech), WIBP-CorV (Sinopharm). The vaccine candidates include Westpac Biopharma, OSE Therapeutics, Jiangsu Rec-Biotechnology/IQVIA, Sanofi/GSK, ReiThera/Leukocare, Scientific and Technological Research Council of Turkey, Moderna, Pfizer/BioNTech, AstraZeneca, Janssen Vaccines, Gamaleya Research Institute, Sinovac, Sinopharm, Anhui Zhifei Longcom Biopharmaceutical and Dynavax[32].

Some of the drawbacks of the approved vaccines include challenges of logistics, slow roll-out, cold chain, and ultracold chain needed for mRNA-based vaccines. This need for ultra-cold chain impedes rolling out these mRNA vaccines in middle and low-income countries[33]. Also, the continuing viral evolution results in mutations that lower immunity induced through vaccination[34]. As observed in other pathogens, escape mutant development may accelerate in the population due to vaccine-induced immune selection [35,36].

Methods

For this review, a literature search was performed using PubMed, Google search engine, Google scholar. Reference lists in the relevant articles were hand-searched to find more articles related to the topic. Keywords used to search related articles were ' SARS-CoV-2', 'COVID-19', ' Pandemic,' 'Immune Response,' 'Vaccination,' 'Vaccine.'

Structure of SARS-CoV-2 Virus

The Coronavirus has been named such because of the spikes that project from the virus's envelope, which gives it a crown-like shape. The envelope has a lipid bilayer which is derived from the host's cell membrane and also has 4 structural proteins that include spike (S), nucleoprotein (N), envelope (E), and membrane (M) (Figure 1). The virus recognizes the angiotensin-converting enzyme 2 to attach to cells, particularly the respiratory epithelial cells of the host [37,38].

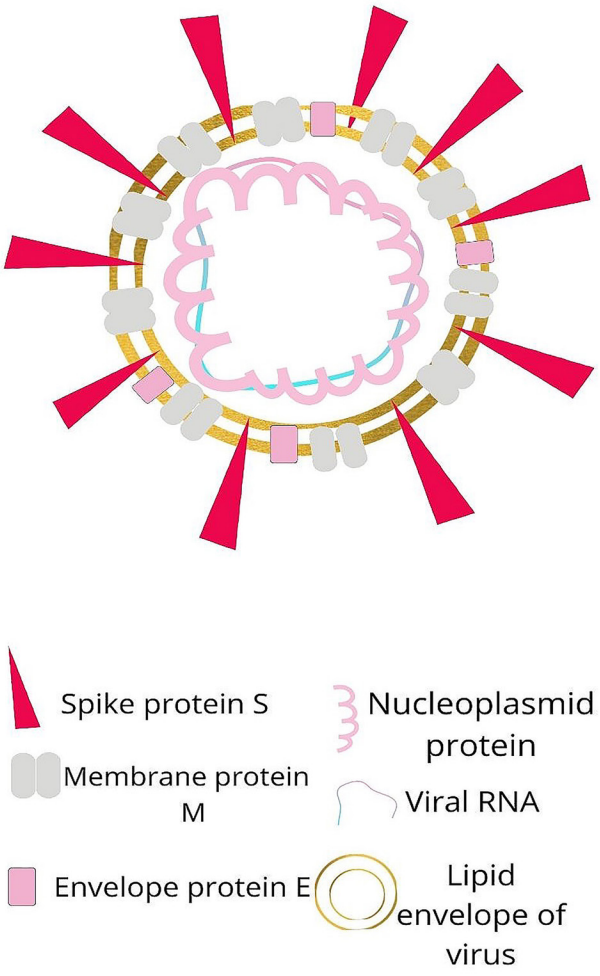

Figure 1: Structure of SARS-CoV-2 virus.

Immune response when infected with SARS-CoV-2

Both humoral and cellular immunity appears to be involved in the immune response to recover from SARS-CoV-2 infection (Figure 2)[39-41]. Antibodies having broad function have been detected at an early stage of infection in subjects hospitalized with COVID-19. These antibodies are aimed at the spike (S) protein of SARS-CoV-2 and have shown a correlation with the survival of the patients[42]. Most of the individuals develop S-protein-targeted neutralizing antibodies (Nabs) following infection. The extent of Nab response has been correlated with viral load and age as the response is higher in individuals with more severe disease and older adult subjects compared to younger adult subjects[43-46]. It has been observed, in studies carried out on the rhesus macaque model, that the Nabs show the strongest correlation with protection[26,47]. Thus vaccines produced for SARS-CoV-2 must be able to cause Nab response[48]. Non-Nabs can also perform a protective function, including antibody-dependent natural killer cell activation, antibody-dependent cellular cytotoxicity, and antibody-dependent phagocytosis[26,42,49]. On the other hand, antibodies that promote inflammation may be responsible for cytokine storms leading to severe forms of the disease[50,51]. Even though most individuals suffering from COVID-19 having mild and moderate disease recover within one week, some suffer severe pneumonia following cytokine storm in the second week. They develop Acute Respiratory Distress Syndrome, disseminated intravascular coagulation, and multiorgan failure within the 3rd week. The cytokine storm is caused by the activation of white blood cells in large quantities, including B cells, T cells, NK cells, macrophage, dendritic cells with the release of the high amount of inflammatory cytokines like IFN . IL 1β, IL 6, IL 12, IL17 [52-54].

Mucosal immunity is perhaps the critical factor in the prevention of infection with SARS-CoV-2. However, there is little available information regarding the response of mucosal antibody in COVID-19 [48] IgA specific to SARS-CoV-2 has been found in saliva and nasal washes of subjects in convalescence that may lower spread of infection from person to person by antibodies' Fc dependent effector function and neutralization [55].T lymphocytes take part in the host response to this infection by killing cells that are infected, giving support for B cell functioning and antibody response and lowering vaccine-induced enhanced disease risk [56,57]. A more vigorous clonal expansion of CD8+ T cells in blood and lungs has been noted in the milder form of the disease and recovery[58,59]. In recovered patients, virus-specific CD4+ and CD8+ T cells, including memory CD8+ T cells, have been found[48, 60]. However, their significance in protecting against reinfection remains unresolved [60-63].T helper 1 cells that produce interferon- are found in acute infection and a less severe form of the disease [41,64]. It has been observed that individuals

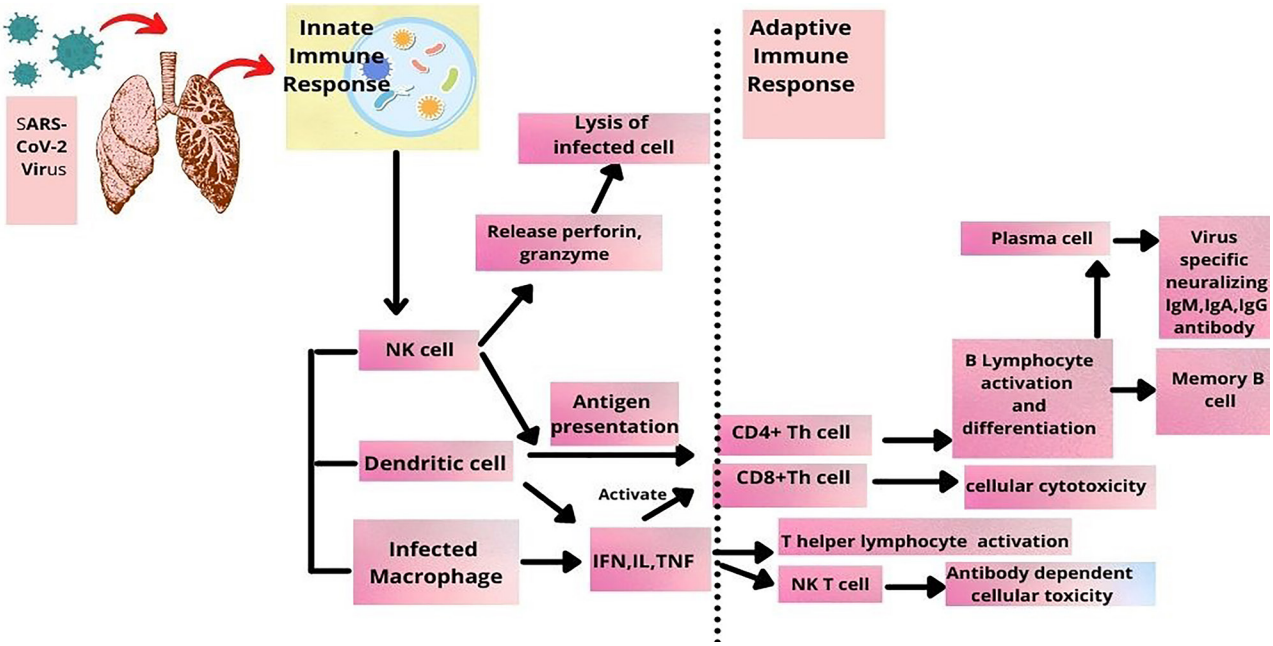

Figure 2: Immune response to SARS-CoV-2 infection

who have interferon- secreting T helper cells against nuclear proteins, membrane proteins, and S protein of SARS-CoV-2 are better protected from COVID-19 infection[65]. The vaccines for COVID-19 intend to induce responses similar to T helper cell phenotype[48]. The more efficient response of T follicular cells helps to increase the number of plasmablasts and increase antibody [66]. Human and animal studies have noted that a strong cytotoxic CD8+ T cell and T helper cell 1 biased CD4+ effector response would provide protection against COVID-19 [67]. SARS-CoV-2, similar to other respiratory RNA viruses, can adopt multiple mechanisms to evade the innate immune response [67,68]. The various mechanisms include type I interferon response inhibition [69-71] at different points, including impairment of viral RNA recognition [72,73] reduction of nuclear translocation of transcription factors of inflammation like IRF3, STAT1, and IRF7 [72,74] and STAT1 and STAT2 phosphorylation suppression[75,76]. Even though several components of innate immunity are significant for protection against COVID-19, type I and type III interferons are centrally relevant [77,78].

Vaccines Formulation and Mechanism of Immune Activation

The vaccines that Moderna and Pfizer have developed apply mRNA technology and lipid nanoparticle system of delivery; AstraZeneca, Johnson, and Johnson, Sputnik V uses recombinant technology in which DNA is transferred into non-replicating adenovirus vector [79-82]. Since the SARS-CoV-2 spike protein S is the primary target for the neutralizing antibodies formed from natural infection and the monoclonal antibodies, both the adenovirus and mRNA vaccines encode this spike protein. The efficacy of Moderna (mRNA-1273) and Pfizer/BioNTech mRNA vaccines for protection against COVID-19 have been noted to be 90-95% [79,80]; the adenovirus vaccine and Sputnik V displayed an efficacy of about 70% and 91%, respectively[81,82]. When measured in blood 2 to 4 weeks after inoculation, both types of vaccine were observed to produce significant titers of neutralizing antibody and virus-specific T cell response[83,84]. A vaccine needs pathogen-specific immunogen and adjuvant for immune response, in which the adjuvant stimulates the innate immune system and gives secondary signal activation of T cells that is part of adaptive immune response[85]. The mRNA present in mRNA vaccines acts as an immunogen (encode a viral protein) and adjuvant, as RNA has immune-stimulatory properties. Once the single-stranded and double-stranded RNA enters the cell, they are recognized by the cytosolic and endosomal innate sensors that form a crucial component of the innate immune response. TLR3 and TLR7 (endosomal Toll-like receptors) bind to single-stranded RNA and inflammasome components in cytosols like RIG-1, NOD2, MDA5, and PKR bind to both single-stranded and double-stranded RNA, leading to cellular activation and formation of inflammatory mediators and type 1 interferon[86,87]. The vitro transcribed single-stranded mRNA of the current vaccines contain modified nucleotide, which decreases TLR and immune sensor binding and thus reduces the excessive formation of type 1 interferon and inhibiting cellular translation [86]. The mRNA is delivered to lymphatics, and protein translation occurs in the lymphnodes[85,87]. The lipid nanoparticles are engulfed by the dendritic cells in the lymph nodes and are eventually form antigen and present to the T cells for adaptive immune response activation[88]. There is the secretion of different cytokines for T cell proliferation and chemokines for T cells recruitment[89,90].

The mRNA vaccines encode the SARS CoV-2 ectodomain with transmembrane anchor and stabilizing S-2P mutation. Therefore, it may elicit antibodies that may be more specific than acquired through natural infection due to spike variation or immune response divergence to the mRNA vaccine instead of infection[19,25]. A study performed in the USA in 2021 shows the difference in the specificity of serum polyclonal antibodies acquired by infection compared to that acquired vaccination with mRNA-1273 observed antibodies elicited by the vaccine are less affected by single spike receptor-binding domain (RBD) mutation than antibodies elicited by infection. Vaccine elicited antibodies were also noted to bind more broadly across the receptor-binding domain, whereas infection-elicited receptor binding domain antibodies focused on an epitope that includes the E484 site. This makes neutralization by vaccine more resistant to RBD mutation. In vaccinated individuals, the antibody response is more homogeneous than convalescent individuals. In those vaccinated, a more uniform neutralizing titer, RBD binding titer, neutralization amount derived from RBD binding antibodies, and mutation on neutralization were observed compared to those convalescent[19]. The mRNA-lipid nanoparticle vaccine produces a different antigen presentation kinetics than viral infection[86,91]. Also, the distribution of antibody

isotopes elicited by mRNA vaccination is different, and fewer of these antibodies cross-react to common cold coronaviruses when compared to that developed through COVID-19 infection [92].

The Adenovirus vaccine, once injected, targets macrophages and Dendritic cells and enhances innate immune response by stimulation of pattern recognition receptors, mainly TLR9, which then causes Type 1 interferon secretion [93]. The Dendritic cells and other cells that secrete Type 1 interferon sends inflammatory and antigenic signals to T cells in lymph nodes activating T cells specific to S protein and stimulates an adaptive immune response against SARS-CoV-2 [85].

A community-based survey carried out in the United Kingdom between December 2020 and May 2021 to assess the effectiveness of COVID-19 vaccination (Pfizer-Biotech; BNT162b2 and Oxford-AstraZeneca; ChAdOx1) for the prevention of SARS-CoV-2 infections observed a reduction in the number of new SARS-CoV-2 infections and the maximum benefit was obtained after receiving 2 doses of vaccine and against high viral load and symptomatic infection [94].

Conclusion

It has been observed from early human trial results that both mRNA and Adenovirus vaccines cause the production of virus-specific neutralizing antibodies and IgG against S protein [83,84]. Vaccination can limit SARS-CoV-2 spread and lead to a return to normalcy. However, the efficacy of vaccines is potentially limited by the appearance of S protein variants. Reservoirs of the disease within human beings and other animals may eradicate the SARS-CoV-2 virus challenge. Formulation of promising vaccines can fortify the immune system and perhaps lead to curtailing the virus and a path out of the world's pandemic.

Recommendation

Formulation of new vaccines with variant S sequence and SARS-CoV-2 proteins can be produced. In order to overcome persistent virus strains, annual SARS-CoV-2 vaccination may be given. Mutant S protein-containing mRNAs can be synthesized and added to LNP carriers and administered in mRNA vaccines. Heterogenicity of immune response to vaccination may be observed when vaccinating mass populations on a global scale. Enhancement of T cell immunity may also be produced by developing and administering vaccines with self-replicating mRNA. Vaccines may therefore be optimized in accordance with the age and immune condition of the individuals.

Consent for Publication

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including issues related to accuracy or integrity

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Author Contribution

The author has developed the concept, study design, execution, data acquisition, analysis, and interpretation. The author performed the drafting, revising, and critical review of the article and gave the final approval of the version to be published: has agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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