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AN OVERVIEW OF THE CONCEPT OF ANTIBODY-DEPENDENT ENHANCEMENT (ADE), AS ADVERSE EFFECTS OF ANTIBODIES, PATHOPHYSIOLOGY AND MECHANISM OF SARS-COV-2 IMPLICATION FOR COVID-19 PANDEMIC OUTBREAK

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ABSTRACT

The severe adverse respiratory syndrome Coronavirus-2 (SARS-CoV-2) and the human immunodeficiency virus (HIV) are recognized zoonotic viruses at a global pandemic scale that strongly considered to be a public health challenge. The Coronavirus 19 (COVID-19) has called for a global mobilization strategy towards the discovery and development of antiviral bioactive agents that are aligned with the viral architectures, biological and immunological properties, a multitude high throughput (HTP) test batteries and potential clinical outcomes. The COVID-19 from its architectural appearance is an enveloped virus, positive-stranded RNA, the envelope spikes mediating cellular entry. The entry process is made of a downstream biological and immunological pathway, with clinical outcomes. The virus-specific antibodies play a very important role in the control of viral pathogenesis. Based on certain circumstances, the presence of virus-specific antibodies can potentially produce different unexpected outcome that produces beneficial effects for the virus. A known example of the harmful activity of the virus-specific antibodies is the antibody-dependent enhancement (ADE) of virus infection. ADE of virus pathogenesis is a concept by which the virus-specific antibodies controls the ingress of the virus into cells through interaction of the crystallizable fragments (Fc) section of the antibodies with complement receptors, and with other cellular receptors. ADE of viral infection has been described *in vitro* in serum samples using a viral infection of susceptible cells that has undergone modification by the addition of virus-reactive antibodies. ADE has been associated to a serious and fatal viral effect that occurs in animals and humans. ADE has been linked to the dengue shock syndrome, which is known as the early death syndrome/phenomenon in laboratory experimental infections of immune animals, and in modified immunoglobulin conditions. Some serious health concerns have been raised for ADE with respect to the discovery and development of vaccines against viruses like the COVID-19 and HIV. This phenomenon has been tested *in vitro* and *in vivo* for many families and genera of viruses that are of public health and veterinary interest. Those viruses share sequence homology, selective replication in macrophages, show a high ability for developing and establishment of resistance, and antigenic diversity. The development of vaccines for COVID-19 has made much progress since the onset of SARS COV2 pandemic, despite the major research challenges. This paper attempts to give an insight into the importance of ADE as a risk of antibody, the different strategies used in the development of vaccines to minimize the risk. The identification approach of viral pathotypes linked with ADE, and the neutralization necessary for viral pathogenesis research. Finally, we attempt to deal with an understanding of the pathophysiology, mechanism of cellular events after the ingress of the virus and the how the effect of ADE is important for the discovery and developing of effective clinical intervention and therapeutic effects.

KEYWORDS: Antibody-dependent enhancement (ADE), SARS CoV-2, COVID 19, HIV, vaccines, pathophysiology, pandemic, drug discovery, Zoonotic viruses.

1-INTRODUCTION

SARS-CoV-2 and HIV are zoonotic viruses on a global pandemic scale now of great public health concern. The Coronavirus (COVID-19) pandemic has led to a global mobilization effort towards the development of potential antiviral agents and the characterization of the viral architectures, studies on bioactive and immunological activities to could produce clinical outcomes.[1] The COVID-19 viral architecture consist of a viral envelope, with a positive-stranded RNA, with the enveloped spikes facilitating the cellular ingress of virus process, downstream biological and immunological pathways that leads to clinical outcomes.[2,3,10]

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The potential development of antibody-based drugs and vaccines for (SARS-CoV-2) has been has made rapid progress through the preclinical and clinical development stages. Results from the study of SARS-CoV and other respiratory viruses indicates that anti-SARS-CoV-2 antibodies could exacerbate COVID-19 through antibody-dependent enhancement (ADE) process.[2,3] Earlier studies on respiratory syncytial virus and dengue virus vaccine showed human clinical safety risks associated with ADE, which can affect vaccine trials.[2,4]

COVID-19 disease development consists of lymphopenia, increased proinflammatory cytokines, and chemokines, buildup of macrophages and neutrophils in the lungs, immune dysregulation, cytokine storms, and the acute respiratory distress syndrome (ARDS).[1,5] Well developed effective vaccines for SARS-Cov-2 have been developed in record time. Many beta coronaviruses, such as SARS-CoV-2 and SARS-CoV-1, increase cellular tropism by the infection of some phagocytic cells (immature macrophages and dendritic cells) via antibody-bound Fc receptor uptake of the virus. The antibody-dependent enhancement (ADE) may be involved in the clinical observation of increased symptom severity linked to early high levels of SARS-CoV-2 antibodies in patients.[2,4]

Children presenting the multisystem inflammatory syndrome (MIS-C) linked to COVID-19 may induce ADE caused by maternally acquired SARS-CoV-2 antibodies bound to mast cells.[4,6] ADE potential risks associated with SARS-CoV-2 have clinical outcomes for COVID-19 and MIS-C treatments, beta-cell vaccines, SARS-CoV-2 antibody treatment, and convalescent plasma therapy for patients.[3,5] SARS-CoV-2 antibodies that are bound to mast cells may be implicated in MIS-C and multisystem inflammatory syndrome in adults (MIS-A) due to initial COVID-19 infection. SARS-CoV-2 antibodies associated to Fc receptors on macrophages and mast cells could show two types of mechanisms for ADE in patients. For SARS-CoV-2, vaccines approval by regulatory bodies for emergency use have been achieved to support the management of COVID-19, although the treatment options are still limited. The current antibody-based vaccines are more effective than the T cell vaccine, which has been successful so far to achieve such a high efficacy, and may be a significant contribution to the current vaccine development. Although ADE has been associated with SARS-CoV-2, the benefits of neutralizing antibodies seem to surpass the ADE effects.[5]

1.1. SARS-CoV-2

The SARS-CoV-2 virus is a betacoronavirus consisting of about 29.9 k RNA bases.[3,5] The SARS-CoV-2 genome encodes three types of proteins, namely; replicate proteins, structural proteins, and accessory proteins.[5] The open reading frame polyproteins (ORF1a and ORF1ab) are cleaved into 16 non-structural proteins namely nsp1-16.[2,6] The SARS-Cov-2, is considered as a virulent zoonotic virus in humans, with a current infection record of about 425 million globally and 5.89 million deaths as of February 20, 2022. The exact nature of SARS-CoV-2 infections and disease etiology, as well as pathophysiology, are still under research investigation. One proposed process in COVID-19 disease etiology included the ability of the nucleocapsid protein to bind to the prostaglandin-endoperoxide synthase 2 (PTGS2)/cyclooxygenase-2 (COX-2) promoter and upregulation of genes expression, leading to increased concentrations of prostaglandin E_2 (PGE_2) and other inflammatory substances.[4-6] The increase in PGE_2 may induce hyper-activation of mast cells linked with increased liberation of histamine and additional inflammatory molecules in COVID-19, predicted as a mast cell disease.[2,6]

1.2. Zoonotic MERS-CoV, SARS-CoV-1, and SARS-CoV-2

Zoonotic MERS-CoV, SARS-CoV-1, and SARS-CoV-2 based on disease progression in humans are known to be evolutionarily linked. The mild variant of the first phase of viral progression, can occur given rise to mild flu-like symptoms.[8] In some patients, infection can evolve to a second moderate-severe variant phase and the progression at this phase coincides with the timing of the occurrence of humoral immunity antibody response from memory beta-cells of cross-reactive antibodies.[6-8] The MERS-CoV studies have demonstrate its ability to infect monocyte-derived macrophages (MDMs), monocyte-derived dendric cells (MoDCs), and T cells.[5,8,9] More studies in mouse preclinical animal models show that phagocytic cells contribute to the antibody-mediated elimination of SARS-CoV-1.[3,9] This procedure has been shown on patients with mild symptoms that did not advance to moderate or severe disease. For patients having moderate to severe symptoms, the pathophysiology is closely linked with infection of phagocytic immune cells (immature MDMs and MoDCs). Chemokines triggers additional dendritic cells and immature macrophages susceptible to cause infection that may lead to a possible amplified infection events of phagocytic immune cells.[5,10] Patients with severe symptoms in some circumstances have shown increased accumulation of macrophages that contributes to the cytokine and chemokine storms,[5,11,12] The SARS-

Cov-2 viruses can affect the adaptive immune responses in a negative manner within an infected population, and infected subjects having high peripheral T cell lymphocytopenia, reduced CD4+ and CD8+ T cells.[4,13-14] SARS-CoV are also associated with T cell apoptosis.[1,14,15] infection of macrophages.[3,16,17] and some T cells with viral dysregulation of cellular pathways, leading to compromised innate and humoral immunity in phase II clinical trials patients.[12,18] The possibility of reducing severity within the body of infected immune cells with high virus titers in the blood can lead to additional disease pathophysiology and clinical observations observed for these viruses.[19] Other disease pathotypes/variations may occur within different cell populations with target host receptors, such as angiotensin I converting enzyme 2 (ACE2) for SARS-CoV-1 and SARS-CoV-2, and dipeptidyl peptidase IV (DPP4) for MERS-CoV.[5,15,20] The increased affinity of the SARS-CoV-2 Spike protein receptor-binding-domain (RBD) as compared to SARS may contribute to the increased airborne transmission of SARS-CoV-2.[5,14,21]

The characterization of the genetic diversity of the viral proteins can give an insight on the design of medical countermeasures (MCMs) for the proper selection of the viral progeny with harmful mutations.[22] Neutral mutations form the basic framework for antigenic drift for the facilitation of escape from immune responses in which the residues can continue to progressively mutate over time.[3,23] The critical-spacer model reveals that proteins may have amino acid residue side-chains necessary to perform some biological functions or possess different side-chains with the potential for positioning or folding of critical residues.[2,24] The genetic variation model of evolutionary protein reveals that the number of critical protein residues is consistent for closely evolved related proteins.[11,25] These concepts are applied to the SARS-CoV-2 Spike (S) protein closely related to coronavirus protein sequences and also provide an insight into viral susceptibility link with designing medical countermeasures (MCMs).[17] The conserved domain of the Spike protein exhibits exposed surface areas with high genetic diversity with an elevated level of risk for antibody-dependent enhancement (ADE). The antibodies targeting SARS-CoV-2, SARS-CoV-1, and MERS-CoV with exposed residues, has been reported through the studies of ADE in animal models and the antibody-facilitated infection of phagocytic immune cells by coronaviruses.[13,14,26] It has also been demonstrated that SARS-CoV-2 antibodies bound to mast cells could be potentially involved in ADE for some Multisystem inflammatory syndrome (MIS-C) and (MIS-A) patients.[5]

1.3. Mechanism of action of ADE

ADE is known to occur by two well defined mechanisms of viral infections: First by an enhanced antibody-mediated virus uptake into Fc gamma receptor IIa (FcγRIIa)-that expresses phagocytic cells, that may result in increased viral infection and replication, or through an excessive antibody Fc-mediated effector functions or immune complex formation, that may elevate inflammation and immunopathology as shown in (Fig. 1, Box 1).[3,27] Both ADE pathways can take place when non-neutralizing antibodies or antibodies at sub-neutralizing levels bind to viral antigens without inhibition of infection.[7,11,12] ADE can be determined in several manner by *in vitro* assays (which are commonly applied for the first mechanism involving FcγRIIa-mediated enhancement of infection in phagocytes, immunopathology, or lung pathology.[11,28] ADE determination by FcγRIIa-mediated endocytosis into phagocytic cells studied *in vitro* has been widely studied for macrophage-tropic viruses in humans.[10,15,29] and feline infectious peritonitis virus (FIPV) in cats.[16,27,29] From the studies, ADE mechanism, non-neutralizing antibodies are shown to generally bind to the viral surface and traffic virions directly to macrophages, which are able to internalize the virions to become very infected.[7,13]

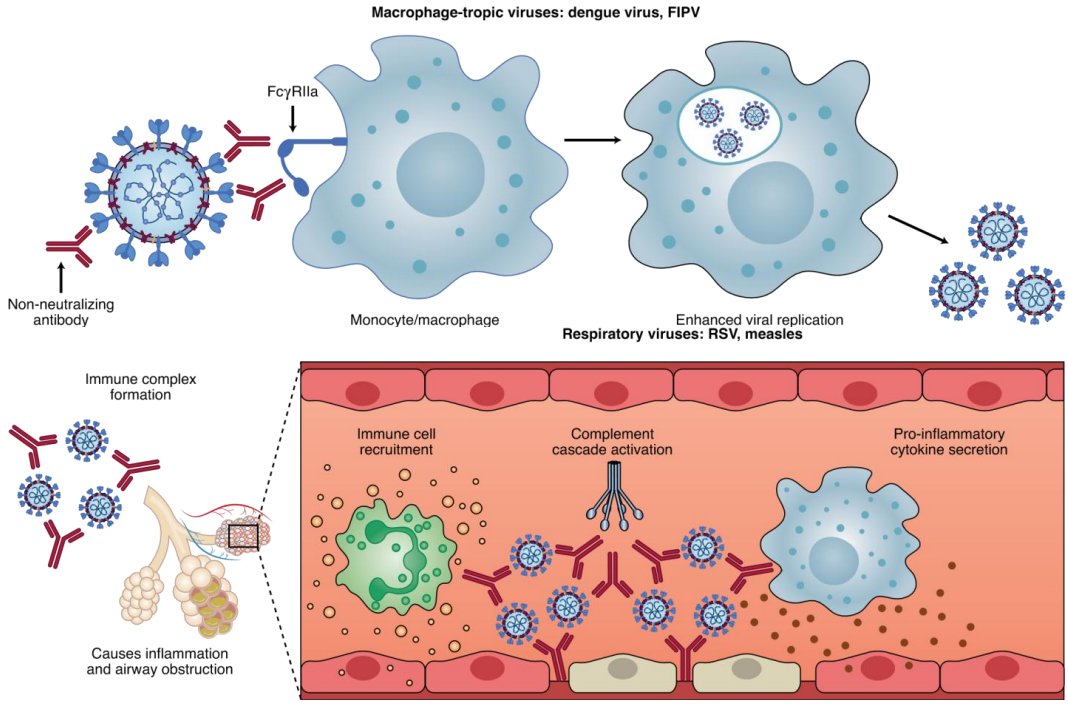


Figure 1: Two important ADE mechanisms in viral disease progression. a, for macrophage-tropic viruses like dengue virus and FIPV, non-neutralizing or sub-neutralizing antibodies contribute to increased viral infection of monocytes or macrophages via FcγRIIa-mediated endocytosis, thus leading to more severe disease occurrence. b, for non-macrophage-tropic respiratory viruses like RSV and measles, non-neutralizing antibodies could establish immune complexes with viral antigens inside airway tissues, leading to the secretion of pro-inflammatory cytokines, immune cell recruitment, and activation of the complement complex processes in the lung tissue. The development of potential inflammation process may lead to airway obstruction triggering acute respiratory distress syndrome (ARDS) in severe cases. COVID-19 immunopathology studies are still in progress, and the most current data available shows that human macrophage infection by SARS-CoV-2 is unproductive. More evidence reveals that immune complex formation, complement deposition, and local immune activation present the most likely ADE mechanisms in COVID-19 immunopathology.[3,30,75]

2.0. CLINICAL VARIATION OF SARS-CoV-2

The variations of amino acids seen in SARS-CoV-2 proteins are known to be consistent with expected natural variations in terms of random mutations and selection of host immune responses. The Spike protein S1 extended domain demonstrates the highest number of exposed surfaces and highly diversified residues.[1,16,31] These spacer residues may contribute to the exposed antigens for antibody responses, with the tendency to suppress immune responses to less immunogenic surface antigens.[5,28,32] Many of the Spike protein antigens may result to non-neutralizing antibodies and mutations at these residues can possibly give rise to antigenic drift to escape immune responses. With the progress of COVID-19 pandemic Spike mutation variants are building up leading to the design of vaccine booster shots before the initial population vaccinations.[5,29,33] The Spike protein is an important and dynamic vaccine target similar with the yearly influenza vaccine hemagglutinin and neuraminidase targets, as the COVID-19 pandemic has persisted with the potential of rapid virus pathogenesis evolution in humans.

2.1. Multiple Coronaviruses Approaches for Cell Infection

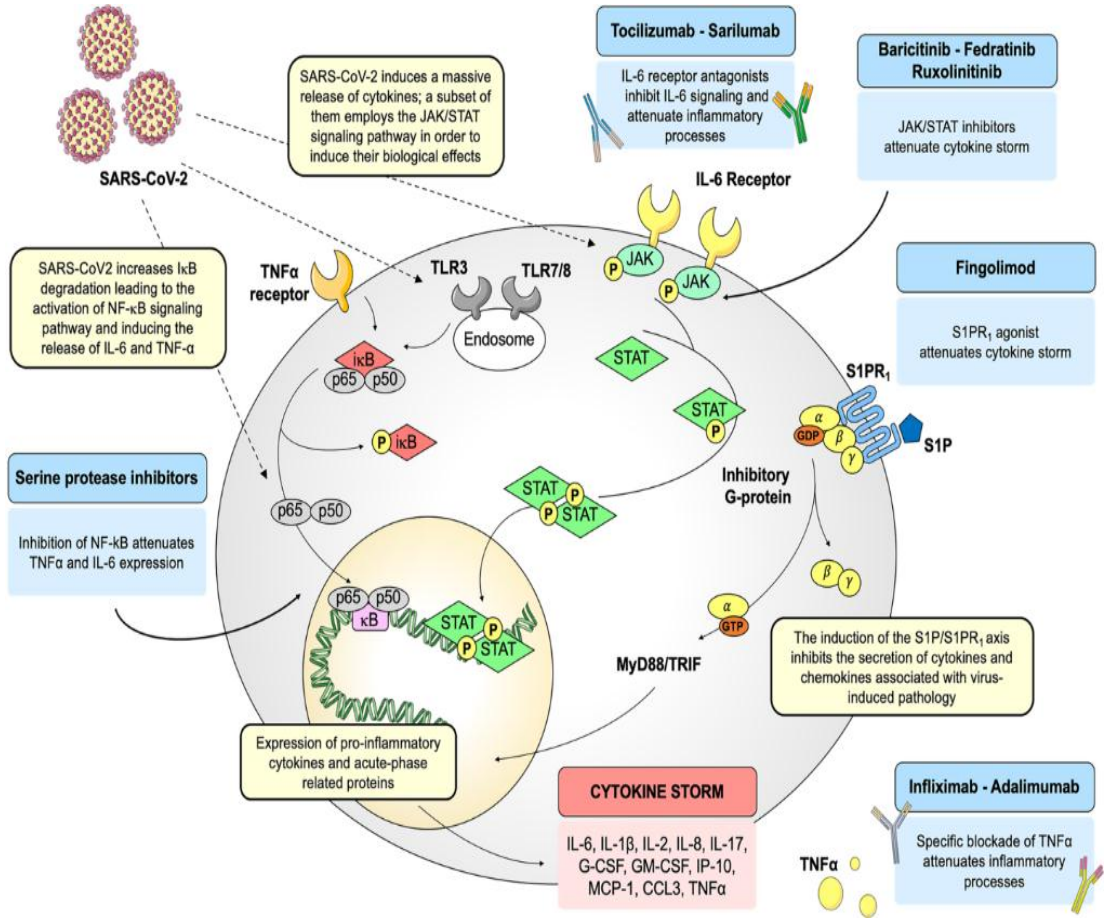
Coronaviruses have the ability for several ways of infecting cells through the direct receptor binding and by indirect antibody Fc uptake. The SARS-CoV-2 Spike protein have receptor-binding domains (RBD) targeting human angiotensin I converting enzyme 2 (ACE2),[5,9,32] which is the initial route for infecting host cells. To exploit the antibody responses, coronaviruses can exert antibody Fc uptake to infect some phagocytic immune cells.[12,33] Coronaviruses are capable to exploit the Spike protein subunit 2 fusion peptide (FP), heptad repeat 1 (HR1), and heptad repeat 2 (HR2) to infect immune cells by the cleavage of Spike within endosomes. At membrane fusion, HR1 and HR2 fuse to form a canonical 6-helix bundle.[34] It is shown that antibody-mediated infection is dependent mainly on Fc receptor II and not the endosomal/lysosomal pathway used by ACE2 targeting. Viral infection of complement receptor (CR) cells is reported as another possible route of infection, that increases the possibility of cellular tropism.[35] The expanded cellular tropism mechanism increases the chances of coronaviruses like SARS-CoV-1, MERS-CoV, and SARS-CoV-2 to have more than one possibility for infecting host cells. Some predictions has been made of the antibody-mediated uptake of viruses to

be the potential mechanism that can induce ADE to cross-reactivity antibodies, maternally transferred antibodies (matAbs), and vaccines.[5,36-38]

2.2. Macrophages and Immune Dysregulation

Macrophages are considered to play an important role in disease etiology immune dysregulation in SARS-CoV-2. Lymphopenia is a clinical feature in subjects with SARS.[5,12,39] and COVID-19.[40] Direct infection of subpopulations of immune cells can occur if they can express virus target receptors. Two receptors have been identified for SARS-CoV-1, including ACE2.[5,41] and C-type lectin domain family 4-member M (CLEC4M, CD209L, CD299, DC-SIGN2, DC-SIGNR, HP10347, and LSIGN),[42] with CLEC4M highly expressed in human lymph nodes.[32,43] Studies conducted on a mouse animal model showed that depletion of CD4+ T cells can lead to increased immune-mediated interstitial pneumonitis when infected with SARS-CoV-1.[44] However, depletion of CD4+ and CD8+ T cells and antibodies can enhance the innate defense mechanisms in controlling the SARS-CoV-1 virus without immune dysregulation.[4,11,45] Similar results were reported in mice with the SARS-CoV-1 infection, but treatment with liposomes containing clodronate, that can deplete alveolar macrophages (AM), inhibited immune-deficient virus-specific T cell response.[21,46] These studies contribute in an understanding of the inter-relationship between antibodies and macrophages to ADE responses in animal models.[5,14] By using the example of macaque model, anti-spike IgG has been shown to cause acute lung injury by changing macrophage response towards proinflammatory monocyte/macrophage recruitment and accumulation during acute SARS-CoV-1 infection.[4,47]

FcR have been shown *in vitro* to block the production of proinflammatory cytokines in human-activated macrophages.[8,32,48] CD169+ macrophages also have ACE2 and are susceptible to SARS-CoV-2 infection.[49-50] SARS-CoV-2 infection have been demonstrated the ability to infect both M1 and M2 macrophages.[8,46] that could be associated with antibody-dependent enhancement of coronavirus infection of macrophages.[12,51] The pathophysiology of moderate and severe SARS and COVID-19 diseases conforms with a proposed model of antibody-dependent infection of macrophages as a principal stage in disease progression, from a mild to moderate and severe symptoms, contributing to dysregulated immune responses.[17,52] This process may involve apoptosis for some T cells and T cell lymphopenia, a proinflammatory process with macrophage accumulation, and the accumulation of cytokine and chemokine in the lungs leading to a cytokine storm in some patients. As illustrated in figure 2, infected phagocytic immune cells may facilitate the virus's transmission to additional organs prior to viral sepsis.



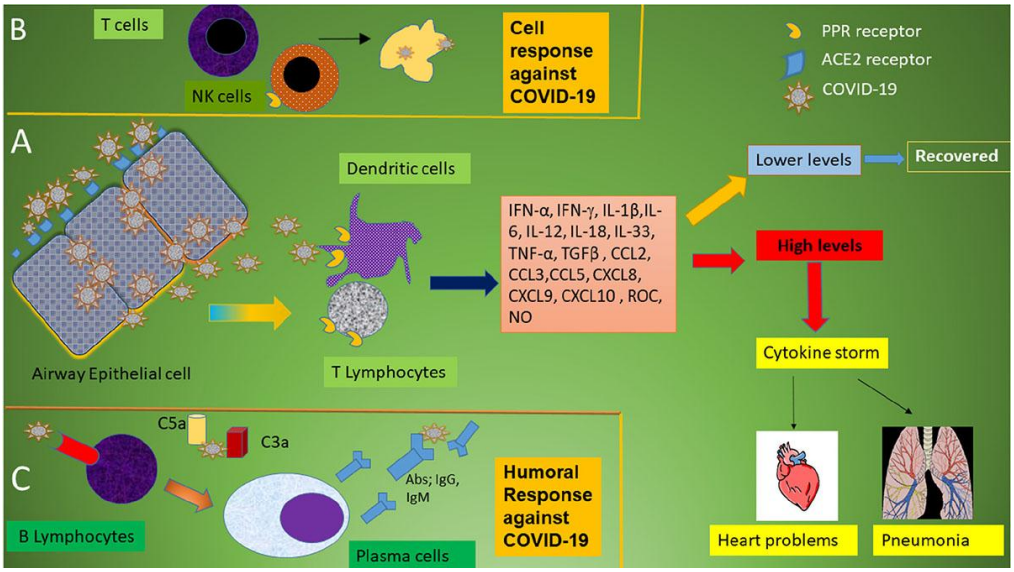


Figure 2: Disease progression model with normal immune responses during the initial mild symptoms phase (see 1–3). Antigen-presenting cells migrate to the lymph nodes to activate T cells (2a). The progression rate to moderate and server disease is the infection of phagocytic immune cells (3a) leading to immune dysregulation (4b). In the lungs, chemokines attract additional dendritic cells and immature macrophages that are subsequently infected in a positive feedback-loop infection cascade (4b). Infected phagocytic immune cells disseminate throughout the body infecting additional organs (5 & 6). Levels of chemokine and cytokines in the lungs from infected cells can create a cytokine storm.[5,8,53]

2.3. Antibody-Dependent Enhancement (ADE) of Coronavirus infection

Antibody-dependent enhancement (ADE) may occur by a series of molecular mechanisms. One model shows that the antibody/Fc-receptor complex has the possibility to mimic viral receptors, giving rise to expanded host cell tropism of some phagocytic cells.[5,11,54] Reports indicates that the number of antibodies used has an effect either on the disease improvement or the inhibition of the virus pathogenesis. Antibodies for one subtype of a virus are known to be sub-neutralizing or non-neutralizing for viral pathogenesis of different strains.[55] Early vaccine results for COVID-19 showed a significant antibody response by day 14,[5,34,57] which represented memory ß-cell responses with cross-reactivity antibodies from other similar coronavirus strain (s). Early high antibody responses were closely linked with increased disease severity for both SARS.[55] and COVID-19 subjects.[25,58] Other research have reported that antibodies from COVID-19 patients can enhance SARS-CoV-2 infections of Raji cells (lymphoma cells derived from ß lymphocytes), K562 cells (derived from monocytes), and primary ß cells.[5,58-59] SARS-CoV-2 infection of some phagocytic cells could be a major entry point to disease progression for some patients.

2.4. Extrinsic Versus Intrinsic ADE.

There are two types of well-defined ADE; extrinsic and intrinsic. The extrinsic ADE involves processes that are external to mononuclear phagocytes, such as the enhanced rates of receptor interaction and internalization of virus-immune complexes.[5,11,60] Extrinsic factors are known to be closely responsible for the adverse effects of dengue ADE-associated pathogenesis until the studies on Ross River Virus (RRV) revealed a different mechanism of action. Incubation of RRV infected cells with anti-virus IgG can lead to long duration ADE mediated persistent productive infection of macrophages due to an innate immune suppression.[5,29] This phenomenon is called intrinsic ADE, which involves the modulation of innate immune effectors through internalization of virus-immune complexes favouring an increased replication and release.[62] Intrinsic ADE therefore, increases the release potential of infected cells i.e., virus released from an infected cell, and extrinsic ADE enhances infected cells mass.[9,62]

2.5. Effects on Virus Replication and Pathogenesis.

Many innate immune effectors are known to modulate dengue hemorrhagic fever and dengue shock syndrome (DHF/DSS), for expanded gene expression of interleukin IL-10 biosynthesis through an intrinsic ADE that can play an important role in the inhibition of host-mediated innate and adaptive immune responses.[5,9,62] Dengue-induced immunosuppression has been illustrated and demonstrated in vitro via the incubation of DENV with serum derived from dengue-infected patients, with an addition of the virus-antibody mixture to THP-1 cells (human monocytic cell line that specifically expresses the FcγR). Dengue-induced ADE has the ability of promoting viral replication and can also induce a TH2-type immune response with elevated levels of IL10 and IL6 synthesis.[9,63] This can result in the high expression levels of SOCS3 (Suppressor of cytokine signaling 3 genes), thus inhibiting the Janus kinase signal transducer and activator of transcription (JAK-STAT) signaling pathway and a possibility to produce IFN-γ.[9] The major implication of this process is the slowdown synthesis of

NO, which can trigger an increase production of dengue viral RNA.[9,48] Other studies using K562 cells (a human chronic myelogenous leukemia cell line) have demonstrated the inhibition of NO synthesis using specific inhibitors to increase virus production during dengue-ADE.[5,9,64]

2.6. Mast Cells Risks for ADE and Multisystem Inflammatory Syndromes (MIS-C & MIS-A)

Mast cells are capable of undergoing degranulation by both IgE and IgG antibodies bound to Fc receptors.[5,65] Cardiac injury condition reported among hospitalized COVID-19 patients are linked to a higher mortality risk.[5,66] Pathological symptoms of heart tissues, on specific cases, have resulted in very sparse interstitial mononuclear inflammatory infiltrates having no major myocardial damage.[11,67] Myocardial damage is principally associated with the fatal outcome of COVID-19.[68] Multisystem inflammatory syndrome in pediatrics (MIS-C) and adults (MIS-A) associated with COVID-19 has been reported in SARS-CoV-2 pandemic outbreaks regions.[5]

The adopted proposed model of MIS-C indicates that the activation and degranulation of mast cells with Fc receptor-bound SARS-CoV-2 antibodies leads to an elevated level of histamine.[5,69] This model is the same with pediatric for MIS-C in children with maternally transferred antibodies (matAbs),[7,23,70] to SARS-CoV-2. For some COVID-19 patients, SARS-CoV-2 nucleocapsid binding to the PTGS2 prompter can lead to elevated levels of prostaglandin E2 (PGE2).[5,34] The rise in PGE_2 levels may play a major in the hyper-activated mast cells that serve as an alternative mechanism for enhancing the increased levels of histamine in older children and adults.[5,9] These increased histamine levels are predicted to reduce blood flow through cardiac capillaries due to constricted pericytes, with an increased risk for cardiac pathology due to cell death by anoxia and coronary artery aneurysms, caused by increased blood pressure.[7,16,70] The case of a 12-years-old child presenting a previous asymptomatic COVID-19 infection, developing MIS-C after a likely second infection has been reported.[21,71]

2.7. Vaccine Risks for Antibody-Dependent Enhancement (ADE)

Virus vaccines are known to exploit messenger ribonucleic acid (mRNA), or deoxyribonucleic acid (DNA), live-attenuated virus pathotypes/strains, inactivated (killed) viruses, protein subunits.[17] Antibodies that are induced by vaccines have the potential to be neutralizing or non-neutralizing, and the non-neutralizing antibodies able to contribute to anti-viral activities, with mechanisms of action used like the antibody-dependent cellular phagocytosis (ADCP), antibody-mediated complement-dependent cytotoxicity (CDC), and antibody-dependent cellular cytotoxicity (ADCC),[61,72] The yearly influenza vaccine can induce both neutralizing and non-neutralizing antibodies that increases protection against the strains in the vaccine and closely related strains. Vaccine-associated enhanced disease (VAED) are reported to take place when there exist several circularizing serotypes of the virus [5, 73] or when the virus exploits the use of antibodies for increased host cell tropism of phagocytic immune cells.

Many viruses linked to ADE possess cell membrane fusion mechanisms.[24] For example, in the case of swine model of influenza A H1N1, vaccine-induced cross-reactive anti-HA2 antibodies can promote virus fusion, that can lead to vaccine-associated enhanced respiratory disease (VAERD).[33,74] Furthermore, ADE has been illustrated for the respiratory syncytial virus (RSV) in the Bonnet monkey model.[3,75]) that has led to some recommendations to avoid the induction of respiratory syncytial virus (RSV) non-neutralizing antibodies or sub-neutralizing antibodies in order to minimize ADE. ADE has also been reported in multiple SARS-CoV-1 animal models.[76] in which a mouse model, an attempt to develop vaccines for SARS-CoV-1 have led to pulmonary immunopathology on infection with SARS-CoV-1.[22,77] These vaccines include inactivated viruses with adjuvant, inactivated whole viruses, a recombinant DNA spike (S) protein vaccine and in a virus-like particle (VLP) vaccine. Severe pneumonia has been identified in mice vaccinated with nucleocapsid protein after exposure with SARS-CoV-1.[46] Enhanced hepatitis was reported in a ferret model vaccinated with a recombinant modified vaccinia virus Ankara (rMVA) that expresses the SARS-CoV-1 Spike protein.[18,78] Report of ADE observed in rhesus macaques with the SARS-CoV-1 vaccine are well documented.[75,79] The SARS-CoV-1 ADE is modulated by spike protein antibodies,[79] and the antibodies to the SARS-CoV-1 spike protein can therefor mediate ingress of viruses via Fc receptor-expressing cells in a dose-dependent manner.[35] It has been reported that the major risk or challenges linked with immunizations against SARS-CoV-1 Spike protein are due to Fc mediated infection of immune cells leading to the prediction of the new manner of creating either SARS-CoV-1 vaccines, MERS-CoV vaccines.[4,80] SARS-CoV-2 vaccines have potentially higher risks of inducing ADE in humans facilitated by antibody infection of phagocytic immune cells.[67] This potential ADE risk is independent of the vaccine technology.[60,81] or targeting strategy selected due to predicted phagocytic immune cell infections upon antibody uptake. For MERS patients, the seroconversion rate can be elevated with disease severity.[9,82] Severe clinical exacerbated outcomes for SARS patients take place simultaneously with the timing of IgG seroconversion.[83] Clinical evidence of early high IgG responses in SARS patients is associated with disease progression.[12,84] and severity.[54,67] Due to a potential safety signal and unfavourable risk-benefit profile.[1,7] antibody treatments for critically ill COVID-19 patients have been halted. Current SARS-CoV-2 vaccines appear seems promising to render protection with high antibody titers; and it is worth noting that the possibility of ADE

risks associated with waning titers of antibodies over time is still not known.[3]

3.0. Convalescent Plasma Therapy

Convalescent plasma therapy involves recovery or acquiring of antibodies from COVID-19 recovered patients then introduce them to patients with active infections. COVID-19 results for convalescent plasma treatment has shown in more studies, unequivocal results with no statistically significant improvement in randomized clinical trials,[19,85] A randomized trial study.[84] showed no significant difference in 28-day mortality (15.7 vs 24.0% odds ratio: 0.59, p = 0.30), and in the placebo trial, advancing to severe disease or all-cause mortality occurred in 44 (19%) convalescent plasma arm vs. 41 (18%) control arm (risk ratio 1.04).[1,85-88] None of the clinical trials studies took consideration of antibody-dependent enhancement within the framework of severe disease progression or all-cause mortality. For SARS cases, a higher discharge rate was reported for patients put on convalescent plasma treatment before day 14 of illness (58.3%) vs. after 14 days (15.6%), $p < 0.001$. The mortality rate for the second group of patients was 21.9%, higher than the overall SARS-related mortality rate of 17% that was reported in Hong Kong.[89] While this study was promising for most patients, the increased mortality above the regional average observed for patients after 14 days of illness was recorded.[1,105]

3.1. Antibody Targets

Reports have shown that the fusion peptide (FP) and the heptad repeat 1 region (HR1) are the main targets for mediating broadly neutralizing antibodies.[1,112] This is due to the understanding of their exposure on the surface of the stem region, also the lack of N-linked glycosylation sites in this region, and conserved domain of the gene sequences,[1,113] Antibodies capable of inhibition of the virus-cell fusion are likely to inhibit the infection of immune cells using Fc-mediated uptake of viruses.[18,114]). This has been illustrated for SARS-CoV-1 for antibodies on the HR2 region.[94-96]). Furthemore, SARS-CoV-2 antibodies that inhibit cell fusion may not confer the same ADE risk like other SARS-CoV-2 antibodies.[115]

3.1.1. Human antibodies targeting parts of Coronavirus spike protein

There have been several reports on antibody response and target regions as the receptor-binding domain (RBD) is the primary target for neutralizing antibodies, followed by the N-terminal domain (NTD). The fusion peptide and the heptad repeat region 1(FP and HR1) play minor roles in the antibody response.[1,98] Generally, people who have not had COVID-19, the infections recorded are usually mild and relatively brief, but their immune systems can provide information on how best to neutralize SARS-CoV-2, the causal agent of COVID-19. A good understanding of the mechanism of neutralizing antibody and potential targets could be a way for researchers to design highly targeted treatments that could help to save the lives of the population with more severe infections.[6,100,116]

Most studies to date conducted on the natural antibodies that block SARS-CoV-2, have focused on those that target the receptor-binding domain (RBD) specific sections of the spike protein for a specific reason. The RBD in the portion of the spike attaches directly to human cells, and therefore, antibodies specifically targeting the RBD are the suitable site to begin the search for antibodies capable of inhibiting SARS-CoV-2.[101] Researchers have associated the spike protein with an umbrella, to the RBD at the tip of the envelop. Although some antibodies bind to the RBD at the tip, many others target more the protein's cap, called the N-terminal domain (NTD).[6,9,117]

Many studies performed on cell culture have demonstrated the N-terminal domain-directed antibodies can potentially neutralize the virus, and can prevent a lethal mouse-adapted version of the coronavirus from infecting mice. This study is useful due to the fact that the NTD is one of the sections of the viral spike protein that can mutate frequently, particularly in several emerging variants of concern, such as the B.1.1.7. The UK variant or strain, and the B.1.351 The South African strain.[5,103] One of the reasons for the effectiveness of these variants to easily invade our immune systems to cause breakthrough infections, or re-infections, is due to the fact that they have can have several mutations beyond the human antibodies that have been most successful in combating the wild/original coronavirus variant.[19,44,104] Studies indicates that about 40% of the circulating antibodies can target another portion of the spike known as the S2 subunit. This finding is promising especially as this portion of SARS-CoV-2 does express less possibility of mutation than the NTD segment, suggesting that S2-directed antibodies could offer a certain level of protection against a wider spectrum of variants.[23,105] Furthermore, the S2 subunit can possibly be an ideal target for a promising pan-coronavirus vaccine for the reason that this section of the spike protein is widely conserved in SARS-CoV-2 and related coronaviruses. These findings are indication of a promising potential for designing COVID-19 vaccine booster shots or future vaccines targeted to combat SARS-COV-2 variants of concern.[106] The findings also support the conclusion that there is a need for a better understanding of SARS-CoV-2 and the immune system's response to neutralize it, thereby making it possible for us to manage the present coronavirus (COVID-19) pandemic and other future emerging viruses.[8,107]

3.1.2. SARS-COV-2 spike protein target for eliciting persistent neutralizing antibodies

The SARS-CoV-2 genome encodes spike (S), nucleocapsid, membrane, and envelope structural proteins. The S protein plays an important role in viral infection and pathogenesis.[1,118] It is made up of subunits

S1 and S2; S1 containing the N-terminal domain (NTD) and the receptor-binding domain (RBD), while S2 contains heptad repeat 1 (HR1) and HR2 as indicated in figure 3a).[7] The SARS-CoV-2 infection undergoes a series of processes which involves first the RBD binding its receptor, angiotensin-converting enzyme 2 (ACE2), to form an RBD/ACE2 complex. This then triggers conformational changes in the S protein, leading to membrane fusion mediated via HR1 and HR2; this process leads to viral entry into target cells (Fig. 3b). The S protein is different from other structural proteins, and this is a crucial target for the induction of antibodies, most especially the neutralizing antibodies, specific for SARS-CoV-2. Antibodies that targets several regions of S protein have different mechanisms of action for blocking SARS-CoV-2 infection. For example, NTD-targeting antibodies (monoclonal antibodies (mAbs) or their segments) are capable of binding the NTD to form an NTD/mAb complex, causing inhibition of conformational changes in the S protein and blocking membrane fusion and viral entry (Fig. 3b). On the other hand, the RBD-targeting antibodies such as mAbs and nanobodies (Nbs) creates RBD/mAb or RBD/Nb complexes that can inhibit binding of the RBD to ACE2, thereby preventing entry of SARS-CoV-2 into target cells (Fig. 3b).[8] An understanding of the mechanism of SARS-CoV-2 infection and the mode of action of anti-SARS-CoV-2-S antibodies is important to better appreciate the kinetics of antibody production in SARS-CoV-2 infected individuals and to facilitate the development of effective prevention. Generally, antibodies targeting the viral RBD are more efficacious than antibodies targeting other regions (such as NTD) of the S protein, but they may have less action spectrum of inhibition of multiple virus strains,[7,81,118]

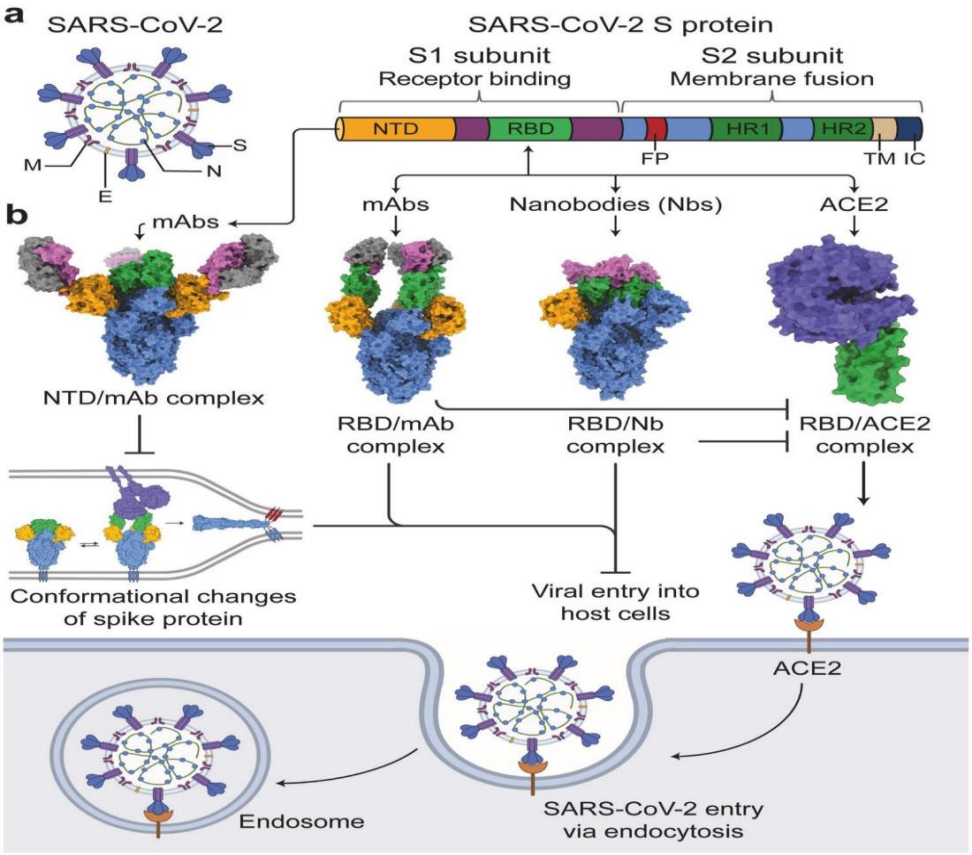


Fig. 3: SARS-CoV-2 spike (S) protein is a key target for eliciting neutralizing antibodies [1, 5] https://pubmed.ncbi.nlm.nih.gov/34801748.

A schematic structure of the SARS-CoV-2 virion and its S protein. M, membrane; E, envelope; N, nucleocapsid. Viral RNA is located inside the virion. NTD= N-terminal domain; RBD= the receptor-binding domain; FP = fusion peptide; HR1 and HR2= heptad region 1 and 2; TM= transmembrane domain, and IC= intracellular tail. In view of the mechanism of action of SARS-CoV-2 S-specific neutralizing antibodies; Monoclonal antibodies (mAbs) targeting S protein NTD inhibit conformational changes of the S protein that are required for S2-mediated membrane fusion and hence inhibit viral entry into host cells. On the other hand, RBD-targeting neutralizes mAbs or nanobodies (Nbs), binding directly to the SARS-CoV-2 S protein RBD and competing with the cellular receptor, angiotensin-converting enzyme 2 (ACE2), result in the neutralization of viral infection and clearance of the virus. The following PDB entries are used for structural illustrations: 7C2L (structure of SARS-CoV-2 S in complex with NTD-targeting mAb 4A8), 7K4N (structure of SARS-CoV-2 S in complex

with RBD-targeting mAb S2E12), 7KKK (structure of SARS-CoV-2 S in complex with RBD-targeting nanobody Nb6), and 6VW1 (structure of SARS-CoV-2 RBD in complex with human ACE2). SARS-CoV-2 S NTD is coloured orange, RBD green, and the rest of the S protein light blue. ACE2 is coloured purple.

3.1.3. SARS-COV-2 spike protein target for eliciting persistent neutralizing antibodies that neutralizes omicron.

Researchers have identified antibodies that neutralize omicron and other SARS-CoV-2 variants.[7,118] These antibodies target sections of the virus spike protein are conserved and unchanged even with mutation of the virus. With the ability to identify the potential targets of the broadly neutralizing, antibodies on the spike protein, it is possible to design vaccines and antibody therapy that can be effective not only for the omicron variant but also for other variants that may develop in the future.[9,33,119] The finding reveals that by focusing on antibodies that target these highly conserved domains on the spike protein, there is a possibility of overcoming the virus constant evolution or mutation.[5,7]

The omicron variant has 37 mutations in the spike protein, which it uses to attach and invade cells to produce an unusually high number of mutations.[9,119] It has been reported, that these changes explain partly why the variant has successfully spread so rapidly, infecting subjects who have been vaccinated and re-infecting those who have previously been infected.[5,9] To evaluate the effectiveness of these mutations, the researchers engineered a disabled, nonreplicating virus, known as pseudovirus, to produce spike proteins on its surface, as coronaviruses do. They then produced pseudoviruses that had spike proteins with the omicron mutations like those found in the early detected variants identified during the pandemic. The first investigation was to understand how well the different versions of the spike protein were able to bind to the protein on the surface of cells, which the virus uses for attachment to enter the cell. This attachment protein is called the angiotensin-converting enzyme-2 (ACE2) receptor.[7] It has been demonstrated that the omicron variant spike protein is able to bind 2.4 times better than the spike protein found in the virus isolated during the onset the pandemic.[9,120] There is not a major increase, compared with the SARS outbreak in 2002-2003, where mutations in the spike protein that increased affinity were associated with higher transmissibility and infectivity. Reports also show that the omicron variant was able to bind to mouse ACE2 receptors efficiently, suggesting omicron might be zoonotic in nature, with transmission between humans and other mammals.[9]

Antibodies collected from subjects who had previously been infected and those who had received the Sputnik V or Sinopharm vaccines as well as a single dose of Johnson & Johnson reported no potential to inhibit or neutralize the entry of omicron variant into cells. Antibodies from patients who had received two doses of the Moderna, Pfizer/BioNTech, and AstraZeneca vaccines showed the retaining capacity of some neutralizing activity, highly reduced by 20- to 40-fold, higher than any other variants.[9,104,121] Antibodies from patients who had been infected by SARS-COV-2 and have recovered and then had two doses of the vaccine also showed reduced activity, although the reduction was almost five-fold less, clearly indicating that vaccination after infection is very important. Antibodies from patients' cohorts on dialysis, who had received a booster with a third dose of the mRNA vaccines produced by Moderna and Pfizer/BioNTech, showed only a 4-fold inhibition in neutralizing antibody activity. This is an indication that a third dose is important and highly needed to reduce infection against omicron.[9,102] Only one antibody treatment out of the many screened has currently been authorized or gone through approved for use with patients exposed to the virus. This has had no or had markedly reduced activity against omicron in the laboratory. An exception is known for antibody called sotrovimab, which had a two- to three-fold reduction in neutralizing activity.[9,25]

3.2.ß Cell Vaccine Designs

ß cell vaccines targeting the spike protein cell fusion mechanisms have the highest chance of producing neutralizing antibodies with minimal or no ADE risk, due to antibody binding sterically blocking cell fusion.[1,122] Even with the presence of neutralizing antibodies, other portions of the Spike protein or other SARS-CoV-2 exposed proteins may enable infection of phagocytic immune cells.[17,91]

3.3. T Cell Vaccine Designs

The T cell vaccines that targets SARS-CoV-2 replicase proteins are reported to have the highest chance of avoiding
viral escape by antigenic diversity and accumulation of mutations in variable residues.[1,18,123] One approach for developing a T cell COVID-19 vaccine has been illustrated by some scientist, with the EpiVax EPV-CoV19 being an example of COVID-19 T cell vaccine.[1,90,124]

CONCLUSION

The concept of antibody-dependent enhancement (ADE) of virus infection is very important for virus-specific antibodies that generally mediate the entry of viruses on one hand, the replication of viruses into monocytes/macrophages and granulocytic cells through their interaction with Fc and/or complement receptors. ADE is also considered an *in vitro* serological process whereby viral infection of susceptible cells can be modified by the addition of a virus-reactive antibody (VRA). Some researchers have linked ADE to many severe or fatal viral conditions in animal and humans, including COVID 19, EBOLA, dengue shock syndrome, the sudden death phenomenon conducted in infected experimental animal models, and other vaccines- and

immunoglobulin-modified conditions. ADE has generated a lot of research interest in immune-virus interaction in relation to the discovery and development of vaccines against RNA viruses (Coronavirus, dengue virus, and human immunodeficiency virus), that has become of global public health concern, especially the central point of current pandemic outbreaks.

All indication shows that concerted efforts in the studies on multiple SARS-CoV-1 and MERS-CoV vaccine developments have yielded much success due to the effect of ADE seen in animal models. ADE risks have been associated with antibody levels, which may be reduced with time after vaccination and also when the antibodies are derived from prior exposures to other coronaviruses. In addition, ADE with mast cells could play a vital role in MIS-C in pediatrics cases and the elderly MIS-C and MIS-A patients, to a greater extend. The highly observed tropism of SARS-CoV-2 poses a possible ADE risk in COVID-19 patients with possible disease progression beyond the mild disease stage. Although there has been increased popularity for ADE research, an understanding of its mechanisms, the pathophysiology of SARS COV-2 is still at a promising stage of development. There is a gap in information on the mechanisms and determinants of ADE and its potential role in disease pathogenesis, and its implications for vaccine discovery and development.

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CONSENT

Not applicable

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