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MINI-REVIEW

Role of antibody-dependent enhancement (ADE) in the virulence of SARS-CoV-2 and its mitigation strategies for the development of vaccines and immunotherapies to counter COVID-19

Kumaragurubaran Karthik [a], Tuticorin Maragatham Alagesan Senthilkumar[a], Shanmugasundaram Udhayavel[b], and Gopal Dhinakar Raj[c]

[a]Central University Laboratory, Tamil Nadu Veterinary and Animal Sciences University, Chennai, India; [b]Poultry Disease Diagnosis and Surveillance Laboratory, Tamil Nadu Veterinary and Animal Sciences University, Chennai, India; [c]Centre for Animal Health Studies, Tamil Nadu Veterinary and Animal Sciences University, Chennai, India

ABSTRACT

Coronavirus disease-2019 (COVID-19) pandemic has become a global threat and death tolls are increasing worldwide. The SARS-CoV-2 though shares similarities with SARS-CoV and MERS-CoV, immunopathology of the novel virus is not understood properly. Previous reports from SARS and MERS-CoV documents that preexisting, non-neutralizing or poorly neutralizing antibodies developed as a result of vaccine or infection enhance subsequent infection, a phenomenon called as antibody-dependent enhancement (ADE). Since immunotherapy has been implicated for COVID-19 treatment and vaccine is under development, due consideration has to be provided on ADE to prevent untoward reactions. ADE mitigation strategies like the development of vaccine or immunotherapeutics targeting receptor binding motif can be designed to minimize ADE of SARS-CoV-2 since full-length protein-based approach can lead to ADE as reported in MERS-CoV. The present mini-review aims to address the phenomenon of ADE of SARS-CoV-2 through the lessons learned from SARS-CoV and MERS-CoV and ways to mitigate them so as to develop better vaccines and immunotherapeutics against SARS-CoV-2.

Introduction

Recent pandemic of coronavirus disease-2019 (COVID-19) has been a worldwide problem. COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a new member of coronavirus even though it shares similarities with SARS-CoV, its pathology, immunology and other aspects of the disease are poorly understood. Similarly, there are several speculations revolving around the source of the virus, its intermediate host, spillover events and zoonotic links.[1] Presently, there are no anti-viral drugs and vaccines to prevent and control COVID-19 and hence, supportive therapy is being used to treat patients. The complete lockdown has been followed in several countries to control the rapid spread of SARS-CoV-2. Social distancing, good personal hygiene are recommended to prevent the further spread of SARS-CoV-2 in the community. Symptoms of COVID-19 range from fever, cough, sneezing, dyspnea, headache, myalgia, loss of taste and loss of sense of smell. Asymptomatic cases are higher, hence controlling the spread of the virus becomes a major problem.[1,2]

The morbidity and mortality rates are increasing day by day worldwide warranting an early development of vaccines and immunotherapies to protect humans from this dreadful disease. In the present situation, plasma therapy seems to be a promising option for the treatment of ill patients. Plasma from convalescent patients possesses a higher titer of antibodies that can be used as prophylactic or as therapeutic

treatment for COVID-19. Few reports show promising results on the use of plasma therapy to treat COVID-19 patients but recommend use in the early stage of infection as the end-stage treatment may not prevent mortality.[3,4] Use of plasma therapy in patients at an early stage not only prevents infection but also prevents viral shedding.[4] Considering the usefulness of plasma therapy and that there are over 10,00,000 recovered patients worldwide who could serve as plasma donors, there is a possibility to curtail this disease employing this therapy.

Vaccines against SARS-CoV-2 will help to prevent the naive population from acquiring COVID-19 disease. Several vaccine platforms such as subunit vaccine, DNA vaccine, mRNA vaccine, and others are under consideration for the development of a safe and protective vaccine against COVID-19. In the near future, there will be an array of vaccines lined up for clinical phase trials since several research groups are working on developing the COVID-19 vaccine.[5] To develop a better vaccine and immunotherapeutic agents for the prevention and control of COVID-19, an in-depth understanding of the molecular biology and immunopathology of SARS-CoV-2 is essential. One such important consideration is the antibody-dependent enhancement (ADE) of viruses as seen in Dengue fever.[6] ADE occurs due to preexisting, poorly neutralizing or non-neutralizing antibodies that interact with virions and complement components enhancing the subsequent infection.[7] ADE has also been documented in other coronaviruses like feline

CONTACT Kumaragurubaran Karthik ✉ karthik_2bvsc@yahoo.co.in 🖃 Central University Laboratory, Tamil Nadu Veterinary and Animal Sciences University, Chennai 5, India

infectious peritonitis (FIP) virus, SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV).[8–10] Hence, due consideration regarding ADE is necessary while designing vaccines and immunotherapeutics for SARS-CoV-2. This mini-review addresses the problems associated with ADE of viruses, lessons learned from SARS-CoV and MERS-CoV, hypothesis on ADE of SARS-CoV-2 and ways to mitigate them so as to develop better vaccines and immunotherapeutics against SARS-CoV-2.

Antibody-dependent enhancement of viral infection

Antibody-dependent enhancement is an event where preexisting, non-neutralizing or poorly neutralizing antibodies increase the subsequent viral entry into cells thereby intensifying the infection.[7] This is a well-documented phenomenon reported by Hawkes in the year 1964 who showed that there was an increase in infectivity of several arboviruses like Japanese encephalitis virus, West Nile virus, Murray Valley encephalitis virus, and Getah virus under *in vitro* conditions.[11] ADE can also occur due to lesser concentration or lesser affinity of neutralizing antibodies. Increasing the affinity or concentration of neutralizing antibodies can alleviate ADE while increasing the concentration of non-neutralizing antibodies can lead to ADE.[12] Under *in vivo* condition, neutralizing antibodies are defined as the antibodies that can prevent viral entry or its fusion without any additional support.[13] Neutralizing antibodies can block the receptor–ligand interaction of virus and simultaneously can network with immunological components leading to clearance of virus from the host.[14] However, when these protective antibodies enhance the pathology of the disease, the phenomenon is called ADE.[15] In clinical settings, this phenomenon has been reported in several important human viruses like human immunodeficiency virus (HIV), dengue virus, respiratory syncytial virus (RSV), ebola virus, zika virus, influenza virus, etc., and also in veterinary pathogens like foot-and-mouth disease virus (FMDV), porcine reproductive and respiratory syndrome virus (PRRSV), etc.[16] Vaccine-induced ADE has been documented in respiratory syncytial virus (RSV), where the formalin inactivated vaccine generated Th2-skewed response and mediated ADE.[17] Several factors like affinity, concentration, specificity and isotype of antibodies are responsible for ADE.[15]

Role of ADE in coronavirus infection

ADE has been reported from the 1980s in feline infectious peritonitis virus (FIPV), an alphacoronavirus highly prevalent among wild and domestic cats. Cats with maternal antibody or received a vaccine against FIP succumbed to virus challenge than did the control animals.[8] It was reported that non-neutralizing monoclonal antibodies (mAbs) or diluted neutralizing mAbs against FIPV spike (S) protein showed enhancement of virus infection while protein A treatment of mAbs prevented enhancement under *in vitro* condition.[18] Thus, antibodies against S protein have a role in the development of ADE in FIPV

infection. Further, 50% of cats passively immunized with anti-FIPV antibodies developed peritonitis when challenged with the same FIPV serotype.[19] This is a contrasting finding as noted in the dengue virus where ADE occurs between different serotypes.

ADE of SARS-CoV

SARS-CoV uses Angiotensin-Converting Enzyme 2 (ACE2) as the receptor for entry into the cells causing respiratory problems. Reports document that SARS-CoV infects immune cells that are devoid of ACE2 and this phenomenon was later linked to ADE.[20] Similar to ADE witnessed in FIPV, the higher concentration of anti-spike protein antibodies neutralized the SARS-CoV while diluted anti-spike protein antibodies increased the infectivity of SARS-CoV which is not observed with anti-nucleoprotein antibodies. Thus, spike protein antibodies have a major role in ADE of SARS-CoV.[9] Though ADE has been documented in SARS-CoV, studies on the role of ADE in human patients are less. Similarly, care should be provided while using mAbs as a therapeutic agent for CoV treatment. mAbs against epitopes in the receptor binding domain (RBD) in the spike protein of SARS-CoV were found to be protective while mAbs that target other epitopes can lead to ADE. mAb43-3-14 is a SARS-CoV mAb targeting the spike protein epitope at 597 – 603 amino acids and found to mediate ADE in non-human primates.[21] Vaccine-associated ADE has been a concern and though vaccine trials in the animal model showed protection, there was Th2 immunopathology with eosinophilic infiltration of the lungs implying hypersensitivity to components of SARS-CoV.[22]

ADE of MERS-CoV

MERS-CoV uses dipeptidyl peptidase-4 (DPP-4) as the receptor for its entry. It was suggested to evaluate MERS-CoV vaccine targeting full-length spike protein since it has the potential to cause ADE.[10] A study conducted on rabbits with MERS-CoV led to the development of non-neutralizing antibodies which caused enhancement of infection during the subsequent challenge. Similarly, passive immunization of naive rabbits with serum from MERS-CoV infected rabbits led to enhanced inflammatory response.[23,24] Since ADE has not been studied completely in MERS-CoV infection, investigations on ADE would throw light on the development of a better vaccine.[25] There was poor cross-protection between SARS-CoV and MERS-CoV antibodies in animal models and rather there were adverse effects.[23,26]

A recent study on MERS-CoV showed that the neutralizing antibodies (mAbs) bind to RBD similar to the receptor (DPP-4) binding and this binding causes ADE. Binding of neutralizing antibodies to RBD can cause a conformational change in S protein similar to receptor–virus interaction. A mAb of MERS-CoV, Mersmab1 binds to the RBD, stabilizes it and causes a conformational change in the spike thereby exposing the S2′ for proteolytic cleavage similar to DPP-4 receptor.[27] Similar reports were observed in SARS-CoV, where S230 (mAb specific to RBD of SARS-CoV) binds to the receptor, stabilizes the RBD and caused a conformational change to expose the

S2′.[28] Sub-neutralizing or an intermediate dose of mAb can cause ADE. The authors conclude that under *in vivo* condition, ADE can occur based on the affinity of mAbs and also on the concentration of the antibody. Hence, to mitigate the problem of ADE caused by neutralizing mAbs, mAbs or vaccines can be designed targeting spike protein other than RBD.[27]

Role of ADE in SARS-CoV-2: what has been learned so far?

Presently there is no proof that ADE occurs in SARS-CoV-2 infection still there are various hypotheses as per the earlier reports of SARS and MERS-CoV and also with few *in vitro* studies with SARS-CoV-2. The ability of the antibody to neutralize the virus has a role in the production of ADE. Antibodies that bind with higher affinity to RBD of S protein of SARS-CoV can prevent virus-ACE2 binding thus preventing entry of the virus. Higher affinity neutralizing antibodies even at minimal concentration can protect infection and does not undergo ADE.[29] Recent finding documents that stronger IgG antibody response against nucleocapsid protein of COVID-19 patients showed a delay in virus clearance while there was an increase in the severity of the infection. Further, it was found that patients with weaker antibody response to nucleocapsid protein had an early clearance of SARS-CoV-2 virus. Hence, antibodies against nucleocapsid protein of SARS-CoV-2 may not be neutralizing. These findings also contributes to the hypothesis of ADE of SARS-CoV-2.[30]

The IgG antibody bound viruses can be taken up by immune cells like monocytes, macrophages and B cells that possess Fc receptors.[9] This uptake increases the virus load instead of clearing the viruses thus causing ADE. ADE is mediated by Fcγ receptor mainly by CD32. A study shows that ADE of SARS-CoV does not use endosomal/lysosomal pathway as used by ACE2 during normal virus transport into the cell.[31] Thus, a new cell entry mechanism is utilized during ADE. The CD32a is expressed on alveolar macrophages and once IgG: virus complex interacts with this receptor, there is proinflammatory cytokine release.[32] There is a hypothesis that age-related COVID-19 infection may be related to the presence of a higher amount of C-reactive protein (CRP) in adults than children and CD32a is also the receptor for CRP.[33,34]

ADE in the case of SARS-CoV-2 can occur due to the priming caused by other coronaviruses, leading to development of non-neutralizing or poorly neutralizing antibodies. SARS-CoV-2 had shown 79% identity with SARS-CoV and about 50% with MERS-CoV based on whole-genome analysis while there was 87.99% identity with bat-SL-CoVZC45.[35] Based on the S protein amino acid sequences, there was 76% identity between SARS-CoV and SARS-CoV-2.[36] The similarity at the amino acid level suggests that there may be cross-reactive epitopes between the two SARS-CoVs. Spike proteins epitopes of SARS-CoV, 447–458 and 789–799 were found to be antigenic and evaluated for the development of vaccines.[37] SARS-CoV-2 shares 72.7% similarity with 447–458 and 100% similarity with 789–799 epitopes of SARS-CoV. Other epitopes of SARS-CoV spike protein that do not share similarity with SARS-CoV-2 may be involved in ADE phenomenon.[38] Though there are few similar epitopes in the spike proteins of SARS-CoV and SARS-CoV-2, there is no clear understanding regarding the effect of non-neutralizing antibodies generated against SARS-CoV to induce ADE of SARS-CoV-2. As several bat coronaviruses share more similarity with SARS-CoV-2, there may be chances that prior exposure to such viruses can elicit ADE of SARS-CoV-2.[38] Surveillance on the bat coronavirus infection in humans can enlighten the possibility of ADE in SARS-CoV-2 due to the priming of other coronaviruses.

Due consideration on ADE should be provided while utilizing the SARS-CoV plasma or mAbs for COVID-19 treatment. Though SARS-CoV and SARS-CoV-2 employ the same receptor, their binding affinity differs. SARS-CoV-2 binds 10 to 20 times strongly with ACE2 when compared with SARS-CoV indicating that RBD may be different.[39] Polyclonal antibodies of SARS-CoV RBD were found to cross-react and prevent the entry of SARS-CoV-2 under *in vitro* condition.[40] Another study reported that SARS-CoV specific mAb, CR3022 could bind to RBD of SARS-CoV-2 but did not compete with ACE2 for its binding.[41] Hence, it was concluded that CR3022 bound with a region of the spike protein distal to the RBD recognized by ACE2.[42] Contrarily, recent neutralization study documents that cross-neutralization antibody response was poor between SARS-CoV and SARS-CoV-2, indicating the development of non-neutralizing antibody which may have a role in ADE.[43] CR3022 though binds strongly with the spike protein yet there was no neutralization of SARS-CoV-2 under *in vitro* condition. CR3022 should further be investigated for *in vivo* protection against SARS-CoV-2 in spite of its inability under *in vitro* condition.[42] SARS-CoV-2 RBD immunization in rodent model showed that there was only development of strong neutralizing antibodies against SARS-CoV-2 RBD region and not the ADE.[12] Further studies are required for the identification of human mAbs that could aid in the development of a cross-protective vaccine.[38] Cocktail of mAbs for COVID-19 treatment could also be an option that showed good response in SARS-CoV and Ebola diseases.[44,45] Figure 1 depicts the role of neutralizing and non-neutralizing antibodies in developing ADE of SARS-CoV-2.

Consideration for developing vaccines and immunotherapy for SARS-CoV-2

Different approaches can be used to mitigate the problem of ADE in SARS-CoV-2 infection. As the receptor-binding motifs (RBM) in RBD of SARS-CoV-2 produce neutralizing antibodies, regions other than RBM can be protected by glycosylation of these epitopes.[25] This can prevent the development of non-neutralizing antibodies. Another approach will be developing a vaccine or immunotherapeutic agent targeting only the neutralizing epitopes to produce a better immune response. This approach is called as immunofocusing and targeting only the epitope in the RBD to produce neutralizing antibodies against SARS-CoV-2 (Figure 2). As already reported, a vaccine developed using small S1 domain of MERS-CoV elicited better immunity than the full length S protein without the problem of ADE.[46] Consideration can also be given on the development of a vaccine based on N protein which was also found to be conserved among SARS and MERS-CoVs.[47] The other approach of mRNA vaccine targeting the specific epitope can be developed to produce neutralizing antibodies and already
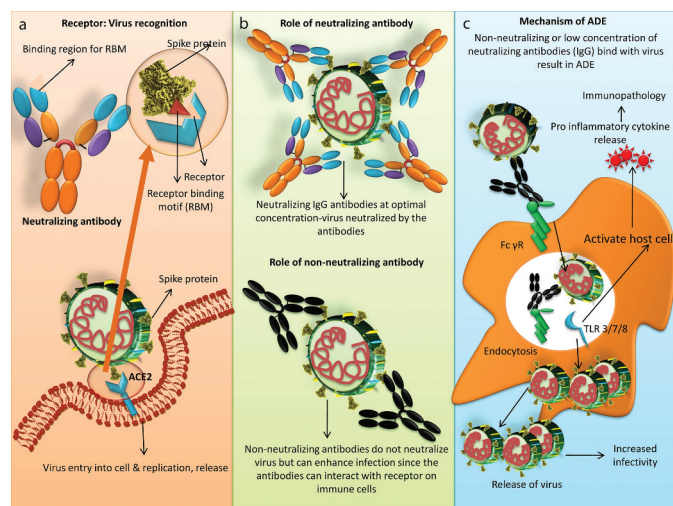
Figure 1. Role of neutralizing and non-neutralizing antibodies in viral infection and mechanism of ADE in SARS-CoV-2. (a) Spike protein of SARS-CoV-2 binds with Angiotensin-Converting Enzyme 2 (ACE2) receptor and undergoes replication. ACE2 recognizes receptor binding motif on the spike protein and the same receptor-binding motif (RBM) is recognized by antibodies. (b) Neutralizing antibodies at optimal concentration neutralizes virus while non-neutralizing antibodies can enhance infection. (c) Mechanism of ADE in SARS-CoV-2. Virus-antibody (neutralizing or non-neutralizing) complex bind to Fcγ receptor on the surface immune cells like monocytes or macrophages leading to virus entry without the use of ACE2 receptor. This leads to increased virus replication and release. Virus-antibody binding to FcγR can also induce proinflammatory response. Viral RNA in the endosomes signal through Toll-like receptor 3 (TLR3), TLR7 or TLR8 activating the host cell to release proinflammatory cytokines which leads to immunopathology.
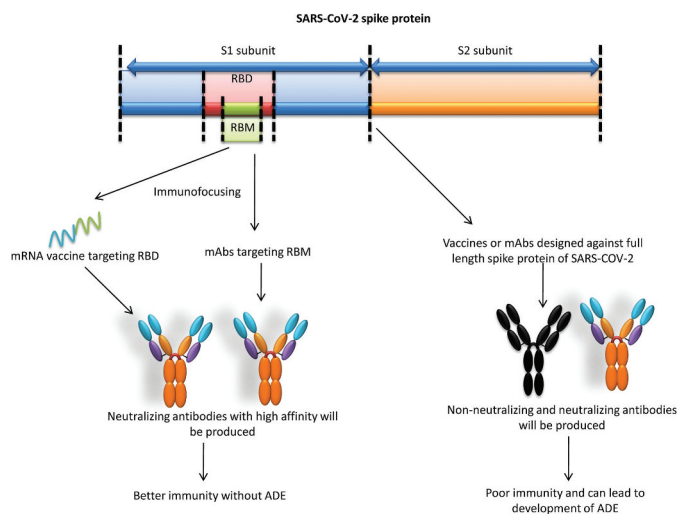
Figure 2. Mitigation strategies of ADE in SARS-CoV-2. Targeting full length spike protein can produce antibody-dependent enhancement (ADE) while immunofocusing or targeting the receptor-binding motif (RBM) can elicit high affinity neutralizing antibodies that can prevent ADE.

focus on this approach has been provided by vaccine developers to produce a better vaccine.[48] Clear understanding of the RBD of both SARS-CoV and SARS-CoV-2 is essential before attempting to develop any cross-protective vaccine. Apart from the choice of antigen target for vaccine development, choice of adjuvant, route of immunization and age at vaccination can also play a role in the development of ADE and immunopathology.[46] Vaccine (formalin inactivated) against the measles virus and Respiratory syncytial virus (RSV) that

stimulated Th2 response was found to induced ADE. Similarly, studies show that SARS-CoV and MERS-CoV vaccine that stimulates Th1 response protected against infection and also the immunopathology.[49,50] Hence, vaccines inducing Th1 immunity can be designed to mitigate the problem of ADE but care should be provided because increased T cell response can also lead to immunopathology.[51]

Similarly, mAbs can be engineered to precision, targeting only the neutralizing epitope thereby reducing the possibility of ADE and hence protecting the host from COVID-19. Engineering antibodies to prevent interaction with FcγRs on immune cells can abolish ADE. Methods like mutation in the Fc region can block the interaction of anti-dengue virus antibodies with immune cells.[7] Another approach is using nanobodies or single-domain antibodies that contain only one variable domain (VHH, heavy chain variable region) instead of the usual two variable domains as they lack the light chain.[52] Nanobodies have various advantages like ease of synthesis, higher target affinity, better tissue penetration, reaches the target site easily due to smaller size and flexibility and importantly due to lack of Fc domain, there would not be a problem of ADE.[53,54] Due to the lack of Fc region half-life of these antibodies will be less requiring multiple doses. Nanobodies can further be engineered as per the need and its cell-penetrating ability can be improved by linking these antibodies with cell-penetrating peptides.[55] Hence, apart from the choice of the epitope for developing mAbs, the platform of mAb synthesis should also be considered to generate safe and protective therapy without the problem of ADE. Technologies like high thorough put peptide scanning approach, hydrogen-deuterium exchange mass spectrometry and other computational approaches can be employed to identify epitopes associated with ADE and epitopes without ADE can be selected for designing vaccines or mAbs. On a cautionary note, identified epitopes devoid of ADE may not be immunogenic thus can fail in the prime function of protection against infection.[56]

Conclusions

In the present context, there is no clear understanding of the SARS-CoV-2 virus, starting from the intermediate host to its prevention measures. Hence, the role of ADE in SARS-CoV-2 is not clear but earlier reports on other coronaviruses caution the complications associated with ADE. Hence, due care should be provided before developing vaccine and mAbs for prophylaxis and treatment of COVID-19. In order to achieve a protective and safe vaccine or immunotherapeutic agent, a clear understanding of COVID-19 dynamics is essential so that targets can be selected appropriately. Studies need to be focused on the immunopathology of SARS-CoV-2 to predict the effect of antibodies on subsequent infection and also to develop a universal coronavirus vaccine. To study the immunopathology, the experimental animal model for SARS-CoV-2 needs to be identified and further studies can elucidate the role of ADE. Strategies like targeting RBM of S protein or targeting other proteins that can elicit high affinity neutralizing antibodies can be used for the development of vaccine or immunotherapeutics so as to minimize ADE. To summarize, an immediate but measured approach is essential for the

development of vaccines and immunotherapeutics that can safely prevent COVID-19 without untoward problems like ADE.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

ORCID

Kumaragurubaran Karthik (iD) http://orcid.org/0000-0002-9215-6306

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