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Review Article
Immune Response and Antibody-Dependent Mechanism Against Viral Infections: SARS-CoV-2 Vaccine as a Case Study

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Abstract

The immune system is a homeostatic mechanism that defends against a variety of infections. To eradicate viral particles/viruses, the immune system of the host uses several immunological responses (adaptive, innate and complement systems). Furthermore, there are well-equipped sensors in the immune system that bring about precise responses and also identify invading pathogens resulting in eradicating multiple copies of new viruses. The host antiviral antibodies play essential roles in the host response immunologically to viral invasions because they neutralize and diminish the virus's contagion. Conversely, the various antibodies that originally protect the host occasionally help the virus infectivity by enhancing their entry and replication in the target cell. The interaction between virus-antibody immune complexes the Fc and/or complement receptors on some specific host cells type which improves the entry of the virus into the host cells is referred to as antibody-dependent enhancement (ADE). Internalized immune complexes affect the host immunological response, enhancing virus proliferation and worsening illness severity. In the research and development of viral vaccines and immune therapeutics, the risk of ADE induction remains a concern to be illuminated.

Key words: SARS-CoV-2 infection, immunological response, COVID-vaccine, antibody-dependent enhancement, pathogens, viral infection, cytotoxicity

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INTRODUCTION

Currently, coronavirus is one of the most popular and deadly viruses around the globe. It has been known to cause severe acute respiratory breakdown and ultimately death[1]. The outbreak of this virus has imposed a threat to global health and the economy as a result of the rapid spread being evident in the increased incidence and mortality globally[2]. SARS-CoV-2, the causal agent of Coronavirus Disease 2019 (COVID-19), has greatly spread over the world, causing significant global morbidity and mortality as well as broad social and economic devastation[3]. HCoV-229E (48%), HCoV-NL63 (49%), HCoV-OC43 (51%) and HCoV HKU1 (52% sequence identity) are all genetically associated with SARS-CoV-2[4]. SARS-CoV-2 is significantly linked to coronaviruses found in horseshoe bats, implying that horseshoe bats constitute the principal carrier, with pangolins as a probable intermediary[5].

Earlier a report has been presented on various myths about the SARS-CoV-2 and how they can be debunked with facts[6]. In like manner, assessment of the knowledge and adherence of the populace to the public health guideline laid out has been evaluated in North and South America[2], Nigeria and Egypt[7] as well as in Africa at large[8]. This has also prompted the evaluation of frugal chemoprophylactic medicinal foods that can play preventive roles in curtailing the virus long before vaccines against SARS-CoV-2 were developed and distributed[9].

The binding of Angiotensin-Converting Enzyme 2 (ACE2), the cellular receptor of viral spike (S) protein, enhances SARS-CoV-2 cells invasion[10,11]. Neuropilin-1 and other host entrance factors have been discovered[12,13] also TMPRSS2, the transmembrane serine protease implicated in the development of the S protein[6]. SARS-CoV-2 S protein has two subunits: The S1 subunit made up of RBD (receptor binding domain) and the S2 subunit (associated with viral entry membrane fusion)[14]. The main focus of treatment research and vaccine is to develop antibodies that hinder S-mediated membrane fusion or ACE2-RBD interactions and COVID-19 virus in the intrusion into the cells of the host.

However, the risk of worsening the severity of COVID-19 via antibody-dependent enhancement (ADE) (Fig. 1a-b) is a potential hindrance in antibody-based treatments and vaccinations. ADE can exacerbate a variety of viral diseases, like respiratory syncytial virus (RSV)[15] and measles[16]. In the case of respiratory infections, ADE is classified as enhanced respiratory disease (ERD), associated with processes unrelated to antibody-like cell-mediated immunopathology as well as cytokine cascades. Also, macrophages-infected viruses, including the dengue virus[17,18] for example Feline Infectious Peritonitis Virus (FIPV), have been shown to produce ADE due to enhanced viral replication[19]. Also, SARS-CoV and MERS-CoV have been shown to cause ADE and ERD *in vivo* and *in vitro*. The contribution of ADE to COVID-19 immunopathology is currently being researched.

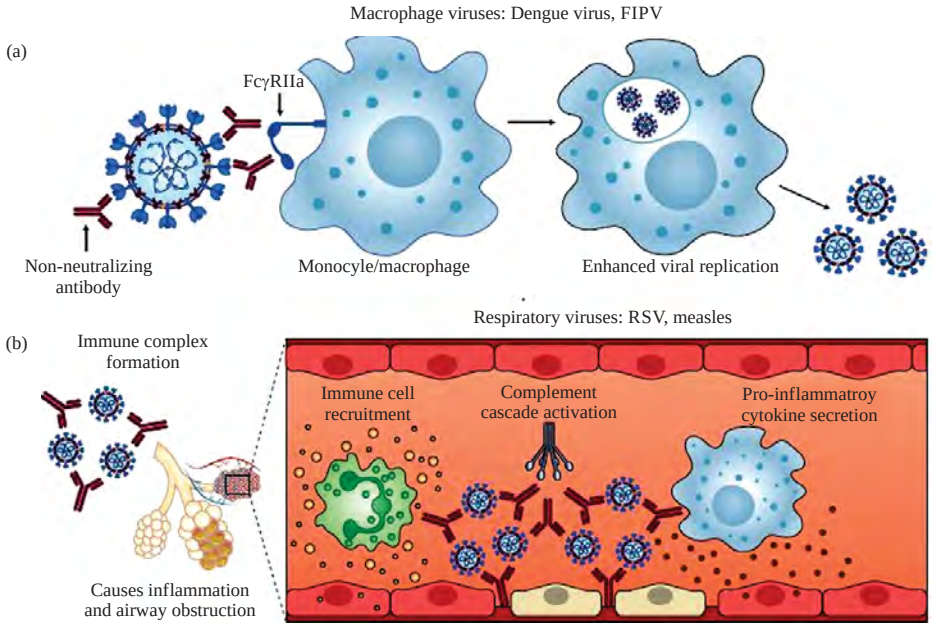

Fig. 1(a-b): Mechanisms of ADE in viral infections[3]

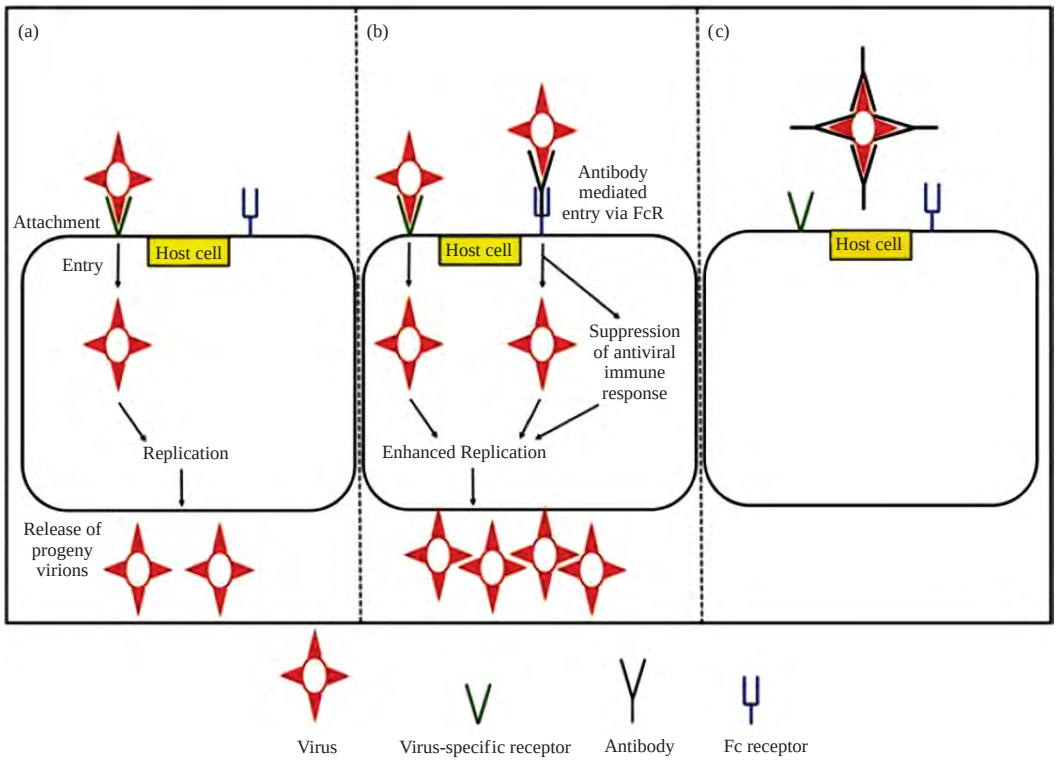

Fig. 2(a-c): Effect of antibody on virus-host cell interaction (adapted)[22]

Viral infection control mediated by antibody: The host adaptive immunological response is dependent on the actions of antibodies to invading pathogens (for example viruses). The major mechanism of antibody-mediated defence is virus neutralization. The antibody activity against viruses is made up of several processes like phagocytosis and the destruction of a viral particle through complement or Fc-mediated effector mechanisms including Antibody-Dependent Cellular Cytotoxicity (ADCC)[20]. The binding of antibody molecules to the epitope surface of the virus leads to neutralization which prevents viral attachment (to the cellular receptor) and access to the host cell as well as post-entry mechanisms including uncoating and fusion, culminating in virion infectivity loss (Fig. 2a-c). The kinetics of neutralization has been described using two models. Regarding the single-hit model, neutralization is achieved by fastening a single antibody molecule to a key spot on the virus. The most recognized multi-hit model states that for neutralization to occur there is a binding between numerous antibodies and virions, above the neutralization stoichiometry threshold. To ascertain the strength of the neutralization, the antibody binding affinity and viral surface neutralization must be available.

Phenomenon of ADE: During the 1960s and 1970s, flaviviruses were discovered to exhibit antibody-dependent enhancement (ADE). The inability of the antibodies binding to the viral particles, leading to its effective neutralization or destruction brings about antibody-dependent enhancement[21,22]. The result of the antibody's non-neutralizing nature (binding the viral epitopes than those involving cellular attachment and entry) or the sub-neutralizing antibody concentrations presence (binding to the viral epitopes below the threshold of neutralization).

In both cases, the antibodies promote virus entrance into the target cells, leading to enhanced viral infection (abnormally high viral infection) (Fig. 2). The virus-antibody immune complexes' internalization into the cells through the interaction of the antibody Fc region with cellular Fc receptors (FcRs) is the ADE basic mechanism[23] hence, FcR-positive myeloid cells such as dendritic cells, monocytes, macrophages and some granulocytes can withstand ADE infection through the uptake of the phagocytic immune complexes. Immunoglobulin (Ig) G mostly initiate ADE, meanwhile, complement antibodies, immunoglobulin (Ig) M and IgA antibodies have been shown to induce ADE according to research[24,25].

Initially, it was thought that the antibody's role in boosting viral infection was restricted to facilitating virus

movement into the host cells, leading to increased infected cell number and thus resulting in greater virus production, in a process known as "extrinsic ADE." Internalized immune complexes on the other hand appear to boost viral replication by suppressing cellular innate anti-viral immune responses, according to research on the Ross River Virus[26,27]. The above-mentioned mechanism is called an "intrinsic ADE" and it is also reported in flaviviruses[28,29]. As a result, ADE is regarded as a complicated process with both intrinsic and extrinsic components that work hand in hand to increase viral infectivity and reproduction. The large release of inflammatory and vasoactive mediators by host cells as a result of increased virus production leads to worsening pathogenesis of the virus and chronic illness.

Due to the risk posed by the magnitude of diseases, in the treatment of viral infections the administration of antiviral immunoglobulins has been considered because of the ADE phenomenon[18]. Similarly, ADE poses a significant problem in vaccination program implementation, since vaccine-induced antibodies could augment viral infection subsequently, increasing the likelihood of severe disease in vaccine recipients. Indeed, safety concerns global first licensed vaccine for dengue virus, "Dengvaxia," have prompted agencies to rethink their mass vaccination plans and give detailed guidelines on safe vaccine application in control programs for dengue virus[30].

Mechanism of ADE: In viral infections, ADE occurs via two major mechanisms, first, through increased viral integration into the Fc gamma Receptor IIa (FcγRIIa)-expressing phagocytic cells, leading to elevated viral load and replication or immune complex generation or high antibody Fc-mediated effector functions resulting in increased immunopathology and inflammation (Fig. 1). Anytime sub-neutralizing or non-neutralizing antibodies attach to the viral antigens without inhibiting or eliminating infections, both ADE pathways can take place. *In vitro* experiments (mostly the first mechanism concerning FcγRIIa-mediated increase of infection in phagocytes), lung pathology and immunopathology are techniques for detecting ADE. *In vitro*, ADE through FcγRIIa-mediated endocytosis into phagocytic cells has been noticed and researched comprehensively FIPV in cats[19] and the human dengue virus (macrophage-tropic virus)[3,31]. The non-neutralizing antibodies attach to the surface of the virus and drive macrophages and virions simultaneously, internalizing virions and causing infection via this mechanism.

Despite their possible efficiency at eliminating cells infected with the virus and their remains, activation mediated by Fc circulating with local innate immune cells like neutrophils, macrophages, natural killer and monocytes dendritic cells could result in unregulated immune activation. ERD and ADE are induced by non-neutralizing antibodies in non-macrophage tropic respiratory viruses for example RSV (respiratory syncytial virus) and measles by causing the deposition of immune complexes in airway vessels and stimulating complement and cytokine pathways, causing obstruction of the airways, inflammation and in chronic conditions, acute respiratory distress syndrome[15,32,33].

These previous ADE observations in measles and RSV are strikingly comparable to COVID-19 clinical manifestations. The complement cascade over-activation (Fig. 3), for instance, has been linked to inflammatory lung injury in SARS and COVID-19 patients[34,35]. From recent studies, researchers discovered that RBD-specific and S- and immunoglobulin G (IgG) antibodies in COVID-19 patients have decreased fucosylation inside the Fc domains-the phenotype linked to a greater affinity for FcγRIIIa, an activating Fc receptor (FcR) mediating antibody-dependent cellular cytotoxicity[36,37]. While increased affinity could be favourable in a few situations due to additional robust FcγRIIIa-mediated effector activities[38,39] deteriorating clinical outcomes have been linked to fucosylated non-neutralizing IgG antibodies that are anti-dengue virus[40]. Larsen *et al.*[36] also found that individuals with acute respiratory distress syndrome and COVID-19 had decreased fucosylation levels in S-specific IgG than individuals with asymptomatic or moderate illnesses. It's still unclear if reduced fucosylation levels in SARS-CoV-2 specific antibodies contribute to the pathogenesis of COVID-19 immunity. SARS-CoV-2 has not been reported to cause macrophages infections in a productive manner[41,42]. As a result, the commonest ADE mechanism related to COVID-19 disease is the generation of antibody-antigen immune complexes[43], which result lead to extreme immune cascade initiation in lung tissue (Fig. 1).

Risk of ADE in SARS-CoV-2 vaccines: In the animal model, the proof of vaccine-induced ADE in SARS-CoV-2 is mixed, raising possible safety issues. Anti-S IgG boosted inflammatory macrophages of pulmonary infiltration leading to severe lung damage in macaques after immunization with an altered vaccinia Ankara viral vector possessing the SARS-CoV-2 S protein, according to Liu *et al.*[44]. They also discovered that the presence of anti-S IgG before the clearance of virus shifted macrophage wound-healing responses into a pro-inflammatory state. In another research, by Wang *et al.*[45], SARS-CoV-2 S protein possessing four B cell peptide epitopes was used to vaccinate macaques and the result showed three among the four peptides induced antibodies against the viral invasion in macaques. However, the fourth

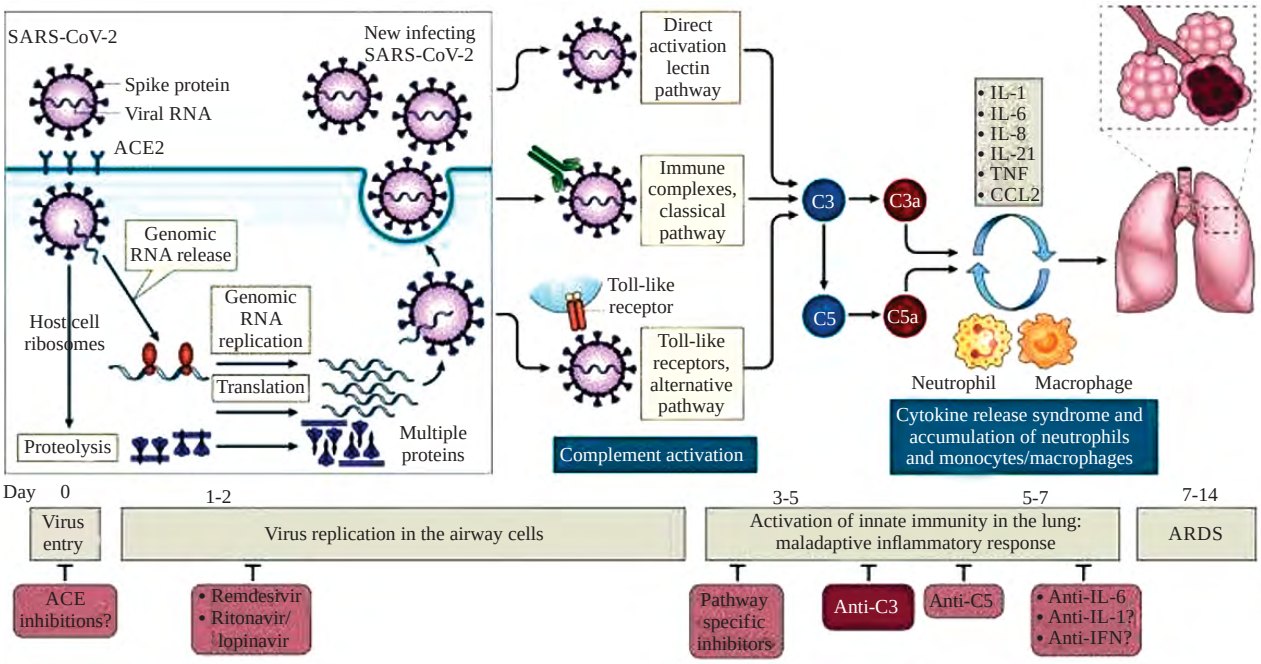

Fig. 3: Complement cascade for the pathogenesis of COVID-19 as described by Risitano *et al.*[43]

It causes inflammatory lung injury in SARS and COVID-19 patients. From recent studies, it has been discovered that RBD-specific and S- and immunoglobulin G (IgG) antibodies in COVID-19 patients have decreased fucosylation inside the Fc domains- the phenotype linked to a greater affinity for FcγRIIIa, an activating Fc receptor (FcR) mediating antibody-dependent cellular cytotoxicity

peptide generated antibodies which enhanced *in vitro* infection leading to chronic lung disease *in vivo*.

Luo *et al.*[46] on the other hand, tested rhesus macaques with SARS-CoV-2 nine weeks after receiving deactivated vaccination, when neutralizing antibody titers had dropped below the level of protection, to see if neutralizing antibodies decreased titers may stimulate *in vivo* infection. While most inoculated macaques became infected after being challenged with a virus, they had lesser viral titers than placebo controls and showed no signs of lung disease.

Similarly, in macaques with decreased neutralizing antibody titers[47], it was discovered that a SARS-CoV-2 vaccine (inactivated) makes cynomolgus macaques susceptible to viral infection and does not cause increased immunopathology in the lungs. Despite increased viral invasion into the B cells through FcγRII *in vitro*, hamsters vaccinated using the recombinant SARS-CoV-2 S protein were defended and prevented lung pathology despite exposure to virus[48].

Thus, depending on the vaccination method used, animal models' immunization of SARS-CoV-2 experiments have yielded outcomes that differ substantially in terms of effective defense, probable ADE and immunopathology. Despite this, vaccinations prompt neutralizing antibodies against the S protein effectively protects animals against SARS-CoV-2 infection and illness not showing signs of infection or disease development[49-51].

These findings showed that human SARS-CoV-2 immunization techniques that cause high neutralizing antibody titers have a high accomplishment rate with a low risk of adverse events (ADE). S-specific neutralizing antibodies could be made by subunit vaccine, for example shows fewer risks of ADE particularly against S stabilized in the prefusion conformation, limiting non-neutralizing epitope presentation[10]. These contemporary immunogen design methods should help to lessen the immunopathology that non-neutralizing antibodies might cause.

Deactivated viral vaccines, which could contain S protein and non-neutralizing antigen targets, which provide numerous non-protective targets for antibodies subsequently causing further inflammation via step-by-step mechanisms noticed in other pathogens related to the lungs, have increased the hypothetical risk of inducing pathologic ADE or ERD. However, a new study on inactivated SARS-CoV-2 vaccine in rhesus macaques, mice and rats showed that it generated high neutralizing antibodies and conferred dose-dependent fortification in rhesus macaques without signs of exacerbated pathology[52]. Increased vaccine research in the Syrian hamster

model, which is more related to the immunopathology of the human COVID-19 than models of the rhesus macaque, may give essential preclinical data in the future[53].

CONCLUSION

To date, clinical studies have not well-proven the action of ADE in human COVID-19. However, ADE risks from immunotherapies via the administration of high doses of effective neutralizing antibodies instead of the administration of lower non-neutralizing antibodies concentration may probably induce ADE. Therefore, it is essential to examine clinical and animal datasets for ADE signs and to put at equilibrium, related ADE safety risks against intervention efficiency in case clinical ADE is detected.

SIGNIFICANCE STATEMENT

In this era of COVID-19, the immunological response as a result of vaccination is vital. Amidst the necessity of SARS-CoV-2 vaccination of the populace to curtail the virus. It is essential to also evaluate antibody-dependent enhancement (ADE) of the severity of the viral infection while enhancing viral entry and multiplication in host cells. Evaluating clinical data is crucial to evaluate ADE and necessary measures ought to be put in place to address ADE risk amongst the general population by prioritizing between high doses of effective neutralizing antibodies and lower non-neutralizing antibodies.

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