Minireview

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Antibody-dependent enhancement of virus infection and disease: implications in COVID-19

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Abstract: Antibody-dependent enhancement (ADE) can be seen in a variety of viruses. It has a deleterious impact on antibody treatment of viral infection. This effect was first discovered in the dengue virus, and it has since been discovered in the coronavirus. Over 213 million people have been affected by the rapid spread of the newly emerging coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). The new coronavirus offers a significant threat and has sparked widespread concern. ADE in dengue virus and other viruses are discussed with possible effect on COVID-19 treatment and vaccine development will need to consider this phenomenon to ensure it is mitigated and avoided altogether. In these case scenarios, the role of ADE and its clinical consequences remains to be explored for this newly detected virus.

Keywords: antibody-dependent enhancement (ADE); coronavirus disease 2019 (COVID-19); implications.

Introduction

Antibody-dependent enhancement (ADE) is a process in which viral-specific antibodies aid virus entrance or replication into antigen-presenting cells containing Fc and/or complement receptors (CRs), such as monocytes/macrophages and granulocytic cells. Hawkes initially identified ADE in Arboviruses, Murray Valley Encephalitis, West Nile Encephalitis, and Japanese Encephalitis in 1964 [1]. Patients who are infected with a single viral serotype (primary infection) develop neutralizing antibodies against that serotype. The pre-existing antibodies cannot completely neutralize the virus if the same patient becomes infected with a different serotype of the same virus (secondary infection). These pre-existing antibodies attach to the virus first, then to the IgG FcRs on immune cells, allowing the virus to enter the cells more easily. Dengue virus, HIV, yellow fever virus, respiratory syncytial virus (RSV), ebola virus, influenza virus, and rabies virus have all been found to show ADE [1, 2]. The fact that these viruses multiply in macrophages, in part or entirely, is a common trait. They generate persistent infection, which is often characterized by long-lasting viremia, by inducing the formation of a large number of non-neutralizing antibodies against the homologous virus. Antigenic diversity is a most characteristics common feature of these viruses, making them partially resistant to antibody neutralization by heterologous isolates. Incompletely neutralizing antibodies (also known as non-neutralizing antibodies) are important in ADE [1, 2].

Several cell surface molecules have been shown to mediate ADE of virus infection, including the FcR, CR, 2-microglobulin, and certain cluster designation (CD) components. Antibody-FcR interaction is also thought to be important in ADE [3, 4]. Internalization of virus-antibody immune complexes into cells via interaction with antibody fragment crystallizable region (Fc region) with the cellular Fc receptors (FcRs) is the mechanism of ADE. As a result, FcR containing myeloid cells including monocytes, macrophages, dendritic cells, and certain granulocytes allow infection to spread by phagocytic uptake of immune complexes. IgG antibodies are the most common cause of ADE; however, IgM antibodies, as well as complement and IgA antibodies, have been demonstrated to cause ADE [4]. Because antibodies play such an important role in host immunity, ADE has generated serious concerns about epidemiology, vaccine design, and antibody-based medicinal therapy. The probable significance of ADE in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its prospective relevance in vaccine development will be discussed in this article.

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ADE in dengue virus

Dengue viruses (DENV) are classified into four serotypes and belong to the Flaviviridae family (DENV-1, DENV-2, DENV-3, and DENV-4). Classic dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) are all caused by them. Fever, headaches, rash, stomach pain, and nausea are all common symptoms of DF. After a dengue virus infection, both humoral and cell-mediated immune responses are mounted effectively against the virus, resulting in the infection's elimination [4, 5]. A substantial number of protective serotype-specific antibodies are produced by the humoral immune response. These antibodies cross-react with other virus subtypes but do not neutralize them, therefore they do not provide protective immunity against them. A second DENV infection with different serotypes can be more severe and life-threatening than the first, and DHF and DSS can develop in this situation, with more severe symptoms (fever, thrombocytopenia, hemorrhagic manifestations, and hypovolemia). Cross-reactive antibodies against distinct DENV serotypes contribute to the development of DHF and DSS by predisposing to increased number of antibodies. Pre-existing non-neutralizing antibodies are acquired from prior infection, passive maternal immunity, and immunization. Natural infection and passive-acquired immunity or vaccinations against one serotype produce cross-reactive non-neutralizing antibodies against other serotypes, causing secondary heterotypic infection to be more severe [5, 6] (see Figure 1).

ADE in coronavirus

Coronaviruses are large positive-sense, single-stranded RNA viruses that cause mild symptoms similar to the common cold and are occasionally associated with pneumonia until the emergence of the Middle East respiratory syndrome coronavirus (MERS), severe acute respiratory syndrome coronavirus (SARS-CoV), and SARS-CoV-2. SARS-CoV-2 is a member of the same beta corona virus genus as SARS-CoV and MERS, however it is associated with less severe infections. Coronaviruses have RNA as a genetic material, as well as nucleocapsid (N) and spike (S) proteins, which help with viral genome assembly, transcription, replication, viral entry, and cytopathic

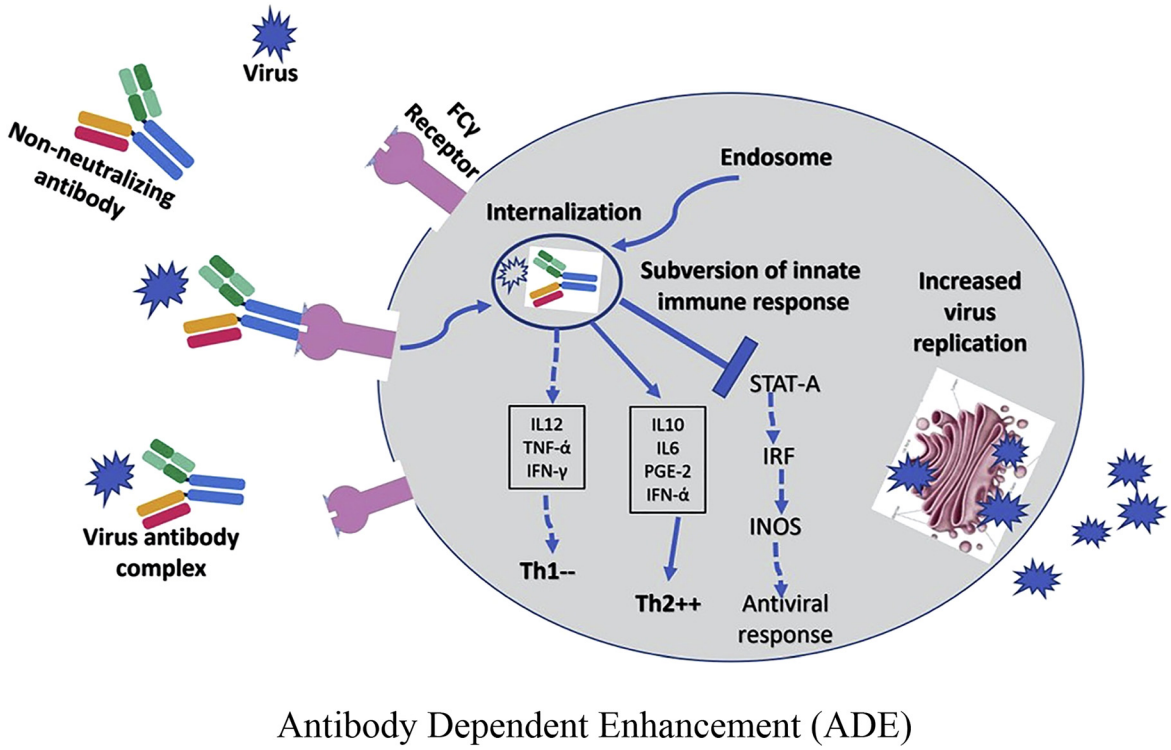

Figure 1: SARS-CoV-2 spike protein interacts to angiotensin converting enzyme-2 (ACE-2) on the host cell surface via the receptor binding domain (RBD) for virus invasion. ACE-2 recognizes RBD on the spike protein and the same RBD is recognized by antibodies. Virus elicits a humoral immune response, which eliminates infection via allosteric and neutralizing antibodies (NAbs) neutralizing antibodies at optimal concentration neutralizes virus while non-neutralizing antibodies can enhance infection and viral replication. The virus-antibody (neutralizing or non-neutralizing) complex binds to the Fcγ receptor on the surface of immune cells such as monocytes and macrophages, allowing virus entry without the usage of the ACE-2. This results in increased virus replication and release. Virus–antibody complex binding to FcγR can also induce proinflammatory response.

effect. The S protein causes viral fusion by attaching to the host membrane's receptor binding domain (RBD). Both SARS-CoV and SARS-CoV-2 use the angiotensin converting enzyme-2 (ACE-2) receptor [7, 8].

MERS inactivated vaccination may cause hypersensitivity, which may progress to lung pathogenesis. The vaccine causes the body to produce neutralizing antibodies and lowers the virus's presence in the lungs. It induces an increase in mononuclear infiltration, eosinophil granulocytes, and interleukin-5 and IL-13 secretion. All of these modifications have been caused by inactivated vaccination. As a result, viral components or pollutants may be the cause of ADE during vaccination treatment [8]. Another key indication of ADE in MERS-CoV is that the virus worsens inflammatory symptoms [9].

Antibodies against the SARS-CoV viral spike protein can cause viral entry and ADE in FcR-bearing cells [8, 10]. SARS-CoV's affinity for FcgRII-bearing cells is increased by these antibodies. The Fc component of anti-spike antibodies and FcgRII on cells are responsible for this rise, and ACE-2 isn't required. Antibodies against the SARS-CoV viral spike protein were also discovered to increase infection in monocytes and lymphocytes, both of which lack viral receptors [11, 12]. Vaccines that produce low antibody titers may not cause ADE after SARS-CoV infection, but highly diluted serum may boost the virus's infectivity. The amount of neutralizing antibody in the blood and the degree of pathological injury in the lungs have been found to be related [13].

Infection caused by a SARS-CoV spike increases viral entrance into cells that express the FcR. It is generally known that when cats are injected with a feline coronavirus spike, infection-enhancing antibodies are produced, resulting in a severe future infection [8, 14, 15]. There is evidence of the molecular mechanism behind coronavirus ADE, but epidemiological data is lacking. For vaccine development and antibody-based therapy strategies, the potential danger of illness aggravation by ADE is a critical problem. ADE in coronaviruses has mostly been observed in cell-based experimental models, unlike ADE in dengue viral infections, which has been supported by evidence over the past four decades [8].

Conclusions

Recovered previously infected coronavirus disease 2019 (COVID-19) patients on infection with another strain are potentially susceptible to ADE. Currently, there are six known strains of SARS-CoV-2, namely, L-, S-, V-, G-, GH-, and GR-strain. The L strain was responsible for causing COVID-19 infections in Wuhan in December 2019. Other strains were subsequently detected; among these, the G strain is responsible for causing most widespread infections [16]. Therefore, if a candidate vaccine for SARS-CoV-2 is specific for any particular strain, then subsequent infection by other strain in the vaccinated person can potentially cause ADE. So, more studies are needed to focus on how the virus interacts with the host leading to the wide variance in observed symptoms and the apparent geographically based discrepancy. Should ADE be proven to be a mechanism of pathogenesis, both treatment regimens and vaccine development will need to consider this phenomenon to ensure it is mitigated and avoided altogether in the case of a vaccine. In these case scenarios, the role of ADE and its clinical consequences remains to be explored for this newly detected virus. Researchers must take note of what is known about ADE and coronaviruses and proceed with extreme caution in the development of the SARS-CoV-2 vaccine.

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