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Mini review

Contribution of antibody-dependent enhancement to the pathogenesis of coronavirus infections

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Abstract: Since the emergence of the SARS-CoV-2 virus in late 2019, vaccines against the COVID-19 infection have been under development using different approaches. At present, protective immunity factors against COVID-19 infection are not completely characterized. Of the four structural proteins of coronavirus, the spike protein (S) and the nucleocapsid protein (N) are most widely expressed in viral infections and elicit the antibody response. Antibody-dependent enhancement (ADE) presents a problem for developing a vaccine against SARS-CoV. It was shown in animal studies that SARS-CoV-1 vaccines containing recombinant S-protein or DNA-vaccine expressed S-protein led to pulmonary immunopathology after infection with SARS virus. Antibodies to the coronavirus S-protein produced by the human immune system in response to infection may contribute to the penetration of SARS-CoV into monocytes and macrophages through the Fc-gamma receptor (FcγR) and may aggravate the course of infection. The demonstration of ADE with coronavirus infection raises fundamental questions regarding the development of vaccines against the SARS-CoV-2 virus and the use of passive prophylaxis or treatment with virus-specific monoclonal antibodies. Evaluation of the mechanisms of immunopathology, including the responses of immunoglobulins and cytokines to vaccines, and tests for antigen-antibody complexes after infection and vaccination can help address these issues.

Keywords: coronavirus infection; SARS-Cov-2; IgG antibodies; antibody-dependent enhancement; Fc receptors

1. Introduction

Since the end of 2019, the SARS-CoV-2 (Severe Acute respiratory Syndrome coronavirus) caused a global spread of COVID-19 infection (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen). SARS-CoV-2 vaccines have been developed using different approaches [1,2], although protective immunity factors against COVID-19 infection are not completely understood.

Coronaviruses (CoV) have been known to people since 1965. Four endemics human CoV: (HCoV-NL63, HCoV-229E (alphacoronaviruses), HCoV-OC43 and HCoV-HKU1 (group A betacoronaviruses) mainly cause mild respiratory infections [3]. Endemic CoV infection accounts for 10 to 30 percent of the incidence rate of annual outbreaks of acute respiratory infections (ARI) [4,5]; serum antibodies to endemic coronaviruses are detected in 65–75% of children after 3 years of age [6].

The SARS-CoV belonging to group B betacoronavirus, caused a dangerous outbreak of severe pneumonia for the first time in 2002–2003. On March 17, 2003, WHO declared an emergency epidemic worldwide due to the spread of SARS-CoV-1 [7]. During the epidemic in 30 countries around the world, 8422 SARS-CoV-1 cases and more than 900 deaths were reported. After the 2012 outbreak in Saudi Arabia caused by group C betacoronavirus MERS-CoV (Middle East Respiratory Syndrome coronavirus), more than 2200 confirmed cases were recorded in 27 countries with an overall mortality rate of 35% (https://www.who.int/emergencies/mers-cov). The clinical features of MERS-CoV infection were characterized not only by rapidly progressing pneumonia and respiratory failure, but also by renal dysfunction, neurological complications and cardiac arrhythmia [8–10]. The envelope spike glycoprotein of SARS-CoV binds to angiotensin-converting enzyme 2 (ACE2) which is mainly expressed on type II pneumocytes, enterocytes of the small intestine, endothelial cells, smooth muscle cells and even in the central nervous system [11]. MERS-CoV used another cellular receptor dipeptidyl peptidase 4 (DPP4), which is expressed on the surface of most body cells [12]. Also, the epidemiology of MERS-CoV differed from that of SARS-CoV. The risk group for MERS-CoV infection includes people who deal with camels, although similarly to SARS-CoV, MERS-CoV also posed a risk to healthcare workers and people who were in close contact with the infected persons [13]. The high epidemic potential of MERS-CoV was demonstrated during the outbreak in South Korea in 2015, when 186 people were infected from one person who came from Saudi Arabia, 36 of infected patients died [14].

A number of vaccines against SARS-CoV and MERS-CoV, both inactivated and on vector platforms, have been developed and tested in preclinical studies, and several candidate vaccines have been studied in humans (NCT03615911, NCT04170829, NCT00099463, NCT00533741), but all went through only phase I of clinical trials [1]. Vaccines against endemic human coronaviruses have not yet been developed, although vaccines against coronavirus infection of pigs and birds are used in veterinary medicine [15,16].

2. Features of protective immunity to coronavirus infection

There are several significant obstacles to developing effective vaccines against human coronaviruses. Despite the repeated appearance of highly virulent coronaviruses in the human population, the role of adaptive immunity factors in recurrent infection is still not well understood. It

is still unknown whether natural CoV infections protect from recurrent infections including diseases caused by highly pathogenic coronaviruses [17,18]. The duration of immunity against CoV infections remains unclear. Finally, it is not known how immunity to endemic coronaviruses affects susceptibility to SARS-CoV-2.

A number of studies related to COVID-19 suggest a protective role for both the cellular and humoral immune responses in humans [19]. In SARS-CoV-1 it was reported that $CD8^+$ T cell responses were more frequent and of a greater magnitude than $CD4^+$ T cell responses. Strong T cell responses correlated significantly with higher neutralizing antibody activity. More serum Th2 cytokines, such as IL-4, IL-5 and IL-10 were detected in the group of nonsurvivors [20].

In transgenic mice, airway memory $CD4^+$ T cells specific for conserved epitope mediate protection against lethal challenge and can cross react with SARS-CoV-1 and MERS-CoV [21]. Current evidence strongly indicated that Th1 type response is the key to successful control of SARS-CoV-1 and MERS-CoV, which is probably true for SARS-CoV-2 as well [22]. Virus-specific T-cell responses are important for CoV eliminating and limiting infection and must be considered when designing CoV vaccines. However, it is still unknown whether only T-cell responses can prevent infection in humans [23].

Of the four structural proteins of CoV, the spike protein (S) and the nucleocapsid protein (N) are most widely expressed in viral infections and elicit the immune response of antibodies [24,25]. In previous SARS-CoV studies, antibody responses raised against the S-protein have been shown to protect from infection in mouse models [26–28].

In regard to the duration of immunity, for SARS-CoV, virus-specific IgG and neutralizing antibodies were reported as long as 2 years after infection [29]. The IgG antibody response in convalescent SARS-CoV-1 patients was detected up to 6 years after infection [30]. One of the significant problems in creating vaccines against SARS-CoV-2 is the unexplained role of antiviral antibodies in secondary infection.

3. An antibody-dependent enhancement of coronavirus infection

Antibody-dependent enhancement (ADE) has been described in some viral infections, with patients developing a severe course of recurrent infections. One of the mechanisms causing ADE is the facilitated virus penetration in combination with IgG antibodies and/or complement factors into the cells, which possess Fc and C3 receptors. This increases virus infectivity and contributes to the development of a severe, life-threatening viral infection. Critical pathogenetic manifestations of viral infection associated with adaptive immunity factors have been described in dengue fever and respiratory syncytial virus (RSV) infections [31,32]. Severe secondary infections were associated with the presence of weakly neutralizing antibodies, which could not prevent a viral infection, but formed immune complexes, causing ADE.

It has long been known that ADE is used by various viruses as an alternative way of infecting host cells. Viruses belonging to the flavivirus family, influenza viruses, RSV, coronaviruses and many others use Fc receptors for infection of cells through ADE [33–38]. Fc receptor is a protein located on the surface of several types of cells of the immune system (natural killer cells, macrophages, neutrophils and mast cells) and takes part in its protective reactions. After binding to antibodies, receptors activate the phagocytic or cytotoxic activity of cells to kill microbes or infected cells by antibody-dependent phagocytosis or antibody-dependent cell-mediated cytotoxicity.

Different classes of Fc receptors, which recognize an Fc portion of IgG (Fc gamma receptors, FcγR) are expressed in many effector cells of the immune system. FcγR mediate various cellular responses, such as macrophage phagocytosis, antibody-dependent cell-mediated cytotoxicity by NK cells and mast cell degranulation. Human FcγR are divided into the classes FcγRI (CD64), FcγRII (CD32), FcγRIIIA (CD16a), FcγRIIIB (CD16b) based on genetic homology. While FcγRI show high affinity for monomeric IgG, FcγRII and FcγRIII exhibit reduced affinity and can form immune complexes [39]. It was recently discovered that, another activating FcRIV receptor that has been identified in mice binds IgG2a and IgG2b immune complexes with intermediate affinity [40].

According to the hypothesis of viral immune pathology in COVID-19, antibody-dependent infection of myeloid leukocytes in the presence of antiviral antibodies leads to the spread of SARS-CoV-2 through the hematogenous route. Multiple virus-antibody complexes stimulate innate immunity components, including complement activation, immune cells and cytokines, which ultimately lead to systemic immune pathogenesis which can cause severe acute respiratory syndrome. On the contrary, a favorable outcome of the disease may occur due to the effective elimination of the virus by cytotoxic T-lymphocytes or with the help of antibodies unable to induce ADE [41].

Usually, after binding to ACE2 receptor SARS-CoV penetrates into sensitive cells by pH-dependent endocytosis [42]. Lysosomal cysteine protease cathepsin L plays a crucial role in achieving effective infection [43]. In contrast, FcR-mediated infection occurs independently of endosomal acid pH or cysteine protease activity [35]. The SARS-CoV-1 virus can infect human monocytes/macrophages that do not carry the ACE2 receptor through the Fc fragment of IgG antibodies [33]. Antibodies to the envelope spike protein which are produced by the human immune system in response to infection may contribute to the penetration of SARS-CoV-1 into monocytes (CD68 +) and macrophages through the FcγRIIA receptor [44]. Therefore, the allelic polymorphism of human FcRIIA was considered as a risk factor for the development of severe pathology in SARS-CoV-1 infection [45].

It was shown that ADE was induced due to anti-spike IgG1 detected in mouse sera, while serum containing anti-spike protein IgG2a was neutralizing and did not cause ADE [35]. *In vitro* studies in human premonocytic cell line showed that the SARS-CoV-1 virus IgG-mediated infectivity depended on antibody titers, since serum with a high concentration of neutralizing antibodies prevented virus entry, while dilution of the serum significantly increased the infection and caused increased cell death [36].

Recently, it was shown that during both SARS-CoV and MERS-Cov, RBD-specific neutralizing monoclonal antibodies (MAb) may functionally imitate the viral receptors thus provoking penetration of coronavirus pseudotypes. It was found that the neutralizing anti-RBD antibody binds to the surface peak protein of coronaviruses instead of viral receptor, triggers a conformational change in the spike and mediates the virus to enter cells expressing the IgG Fc receptor via receptor-mediated pathways [38]. With respect to antibodies to RBD of SARS-CoV-2, it was shown that antibodies to RBD block virus growth, as they do not allow virus particles to infect new cells [46].

ADE presents a problem when developing a vaccine against SARS-CoV since in some cases vaccines can aggravate rather than prevent CoV infection due to the development of eosinophilic pulmonary infiltration which has been observed upon subsequent infection [47,48]. In mice, immunization with vaccines based on both S-protein and N-protein of SARS-CoV-1 led to the development of immunopathological changes in the lungs (up to severe pneumonia) following

infectious virus challenge. Most often pulmonary complications were observed in aged mice [48–50].

When studying vector DNA vaccine on macaques, immunoglobulins IgG directed against the S proteins of SARS-CoV-1 stimulated pulmonary inflammatory reactions and caused acute lung damage after challenge of immune animals [51]. The pathogenic effect of IgG against spike protein was due to an indirect effect on macrophages through the Fcγ receptor.

It is likely that antibody-mediated penetration into cells may aggravate the course of SARS-CoV secondary infection. However, *in vitro* interactions do not necessarily correspond to processes at the body level. The participation of complement at physiological concentrations, which is usually absent in *in vitro* systems, can reduce the ADE caused by various IgG subclasses [1].

In addition, it is necessary to take into account the correct choice of epitopes for vaccine development, since it has been shown that the MAbs which were specific to the lateral site of the receptor-binding site hold the MERS-CoV spike in the down position without thereby activating the increased penetration of the virus into sensitive cells [38]. In order to find broad-spectrum antibodies, the effectiveness of anti-SARS-CoV-2 antibodies from blood samples taken in 2003 from a patient with SARS was tested. Of the 25 antibodies tested, eight were able to bind to SARS-CoV-2 S-protein, and one antibody (S309) was particularly promising. S309 was able to not only bind to the S-protein, but also neutralized SARS-CoV-2 and S-protein-based pseudotypes. Using cryoelectronic microscopy, it was found that the antibody does not bind to the RBD domain, but rather to a nearby site with a length of 22 amino acids. This site was conservative both among SARS-CoV-2 isolates and in other strains of coronaviruses of the same group, for example, RaTG-13 and SARS-CoV. A previous study showed that the S-protein complex can be in closed and open conformation, and S309 successfully binds to both variants [52].

To date, several studies have been published on immunogenicity and protection in animal studies of SARS-CoV-2 vaccines which was developed using various platforms. Thus, the whole-virion inactivated SARS-CoV-2-based vaccine has been studied in mice and macaques [53]. The researchers themselves note that in this study, the possibility of ADE manifestation after a decrease in antibody titers cannot be completely excluded. Promising data have been obtained after studying adenovirus-vectored and micro-RNA-based vaccines in non-human primates when it was not obtained evidence of immune-enhanced disease [54,55]. Nevertheless, the answer to whether or not ADE develops upon infection after vaccination can only be provided by clinical trials.

4. The significance of ADE in human CoV infection

To date, clinical studies examining ADE in patients with CoV infections remain limited. Several studies have not reported a correlation between the clinical outcome and the formation of anti-SARS-CoV-1 antibodies in infected individuals [33] or the positive effects of the formation of neutralizing antibodies to S and N proteins on subsequent recovery [56]. In contrast, other studies have associated an unfavorable prognosis of disease outcome with early seroconversion of SARS-CoV [57,58]. During the COVID-19 pandemic, patients with severe SARS-CoV-2 infection demonstrated faster achievement of peak levels of antibodies to spike proteins, compared to patients who recovered and subsequently had reduced B-cell immunity with week neutralizing ability [56]. It was shown that the prognosis for survival was worse in those patients who had quickly developed a

neutralizing serum antibody response to the virus. Moreover, there were more elderly people among these patients with an early antibody response [59,60].

It should be noted that when patients with SARS-CoV-1 and SARS-CoV-2 were treated with convalescents plasmas, no side effects were reported and a positive effect on recovery was shown [61,62]. These are encouraging results for the possible use of convalescent plasma preparations or the administration of monoclonal antibodies for therapeutic purposes.

Many highly virulent viral infections cause serious illnesses through immune-mediated tissue damage and/or increased vascular permeability caused by an overreaction of the immune system, characterized by an abnormal release of cytokines, often called 'cytokine storm' [63–65]. It has been suggested that dysregulation of host cytokine/chemokine responses is a hallmark of SARS-CoV-2 [65–68]. It was shown that patients with COVID-19 had a significant increase in pro-inflammatory cytokines and chemokines, including tumor necrosis factor (TNF) α, interleukin 1β (IL-1β), IL-6, granulocyte colony-stimulating factor, interferon gamma-induced protein-10, a monocytic chemoattractant protein-1 and inflammatory macrophage proteins 1-α [69,70]. The pathogenesis of the highly severe course of these infections may be attributed not only to the influence of virus proteins on host innate immunity factors, but also could be explained to some extent by the greater virus infectivity via ADE. Viruses complexed with antibodies may involve a wider range of antigen-presenting cells: not only dendritic, but also B-lymphocytes and other cells carrying Fc receptors and capable of attaching the immune complexes. The role of mast cells which also possess Fc receptors and, moreover, hold a powerful arsenal of vasoactive and pro-inflammatory mediators, has not widely discussed in the literature. At the same time, it can be assumed that the activation of mast cells by the virus-antibody immune complexes can lead to a massive release of biologically active substances, vascular damage and a strong aggravation of the patient's condition.

In connection with the above, it would be interesting to explore how ADE can contribute to the pathogenesis of SARS-CoV-2 disease.

5. Conclusions

The demonstration of ADE with infection caused by the CoV viruses raises fundamental questions regarding the development of vaccines against the SARS-CoV-2 virus and the use of passive prophylaxis or treatment with virus-specific monoclonal antibodies. The evaluation of the mechanisms of immunopathology, including the responses of immunoglobulins and cytokines to vaccines, and tests for antigen-antibody complexes after infection and vaccination can help address these issues.

Possibly, when developing vaccines against the new coronaviruses it would be worthwhile to direct attention to vaccines aimed at stimulating the Th1 immune response. Another way to avoid unwanted immunopathological post-vaccination reactions is to adjust vaccination regimens, such as priming boosting, or using Th1 type adjuvants.

And further, a study of ADE pathways for recurrent CoV infections will help identify target points for potential therapeutic agents to prevent possible antibody-related complications.

Conflict of interests

All authors declare no conflicts of interest in this paper.

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