Designing Vaccines and Biologics to Minimize Antibody-Dependent Enhancement of Viral Infections

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For a variety of viruses, patients that have been previously infected by one serotype and are later infected by another can suffer outcomes that are worse than those infected only once, indicating that prior infection can sometimes be the opposite of protective. One explanation suggests that the differences in the two viral serotypes cause the antibodies induced by the first infection to fall short of neutralizing the second serotype and, instead, bridge the second virus to IgG Fc receptors on immune cells. As such bridging is believed to enable viral entry into immune cells, shifting the tropism of the virus (Taylor et al. 2015), the outcome manifests as an antibody-dependent enhancement (ADE) of infection. This has been observed with Dengue virus (Katzelnick et al. 2017), Zika virus (Bardina et al. 2017), Ebola virus (Kuzmina et al. 2018), and, importantly, coronaviruses (CoVs) (Petersen & Poyle 1980, Vennema et al. 1990, Yip 2011, Wan et al. 2020, Tetro 2020). As such, it is especially important to consider in the context of the massive response to the current Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) pandemic, including the development of vaccines and novel treatments for stemming morbidity and mortality. In fact, data from previous CoV
research strongly suggest that ADE may play a role in the virus’s pathology. If this is the case with SARS-CoV-2, then careful design and testing of vaccines or alternative approaches to prophylaxis may be needed to prevent ADE. Here we outline how clinical and experimental observations from earlier CoV outbreaks may suggest strategies that may reduce ADE in treating the SARS-CoV-2 pandemic.

First, clinical samples from the 2003-2004 SARS-CoV outbreak indicate that the virus can infect immune cells, despite the fact that immune cells do not express the ACE2 receptor, which mediates SARS-CoV entry into lung cells (Li et al. 2003, Gu et al. 2005). These results were corroborated by in vitro observations showing that some antibodies that bind spike protein can facilitate uptake by human macrophages and B cells via their Fc receptors (Jaume et al. 2011, Yip et al. 2014). In the case of MERS, Fc-mediated targeting has even been observed with neutralizing antibodies that bind directly to the receptor binding domain of spike protein (Wan et al. 2020). While ADE is believed to primarily target various immune cell populations, it is worth noting that lung epithelial cells have also been shown to express functional Fc receptors (Spiekermann et al. 2002).

Second, while efficacy data on human CoV vaccines is lacking, results from pre-clinical models suggest that some vaccine designs are capable of causing an ADE immune response. For example, when macaques were vaccinated with inactivated SARS-CoV and challenged with live virus, some of the animals exhibited an ADE phenotype, extensive macrophage and lymphocyte infiltration in the lungs and edema in the
alveolar cavity (Wang et al. 2016). In addition, macaques vaccinated with a modified vaccinia Ankara virus expressing SARS-CoV spike were more likely than controls to exhibit acute diffuse alveolar damage and severe acute lung injury upon viral challenge (Liu et al. 2019). Mice and hamsters vaccinated with trimeric spike protein vaccines were protected from SARS-CoV infection but showed evidence of developing ADE antibodies (Kam et al. 2007, Jaume et al. 2012). When four different SARS-CoV vaccines developed for human use were tested in mice (two different whole virus vaccines, recombinant spike protein, and a virus-like particle), they all triggered pulmonary immunopathology upon viral challenge (Tseng et al. 2012). Similar effects were also seen in mice vaccinated with virus replicon particles expressing SARS-CoV nucleocapsid protein (Deming et al. 2006).

Circumstantial clinical evidence for ADE in SARS-CoV patients includes the observation that macrophages treated with the virus and sera from patients that succumbed to the infection produced a cytokine profile that was similar to that observed in macaques that experienced fatal acute lung injury following vaccination and viral challenge (Liu et al. 2019). This effect could be diminished by blocking FcγR, suggesting that, as in the macaque model, this effect as mediated by antibodies. More indirectly, antisera from SARS-CoV patients were protective in viral infectivity assays when used at a high concentration but enhanced infection when highly diluted (Wang et al. 2014).
Whether SARS-CoV-2 can cause ADE effects remains an open question. However, given that the closely related SARS-CoV demonstrated this phenomenon, we believe that this question should be urgently resolved. Furthermore, this risk will likely require that vaccine development efforts should maximize safety with extended testing and or by avoiding epitopes that can give rise to antibodies capable of causing ADE-associated pathologies (Graham et al. 2019). This is especially important in the context of vaccinating the most vulnerable populations such as the elderly, who may have impaired immune responses to vaccines that would result in lower titers of neutralizing antibodies and increased chance of ADE. Apart from vaccine development challenges, monoclonal antibodies and associated approaches should be carefully tested for ADE effects. One powerful potential safeguard could involve mutating the Fc binding domain to retain its neutralizing potential while preventing uptake in immune cells (Kang and Jung 2019). All of these approaches are key to making sure that while we rush to create countermeasures to this deadly disease, we use the full armory of protein design tools at our disposal to rationally minimize possible risks.

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Competing interests

N.E, T.G, M.K, G.M.C., J.T., and H.R. are shareholders and/or employees of Helix Nanotechnologies Inc., which is developing gene-encoded vaccines for SARS-CoV-2. A
full list of G.M.C.’s tech transfer, advisory roles, and funding sources can be found at http://arep.med.harvard.edu/gmc/tech.html. J.T. is a shareholder and employee of SmartPharm Therapeutics, which is developing gene-encoded antibody vaccines for SARS-CoV-2.

References


