Perspective | Published: 09 September 2020

# Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies

Wen Shi Lee, Adam K. Wheatley, Stephen J. Kent & Brandon J. DeKosky

*Nature Microbiology* **5**, 1185–1191 (2020) | Cite this article



## Main

The emergence and rapid global spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has resulted in substantial global morbidity and mortality along with widespread social and economic disruption. SARS-CoV-2 is a betacoronavirus closely related to SARS-CoV (with ~80% sequence identity), which caused the SARS outbreak in 2002. Its next closest human coronavirus relative is Middle East respiratory syndrome-related coronavirus (MERS-CoV; ~54% sequence identity), which caused Middle East respiratory syndrome in 2012 (refs. [1,2]). SARS-CoV-2 is also genetically related to other endemic human coronaviruses that cause milder infections: HCoV-HKU1 (~52% sequence identity), HCoV-OC43 (~51%), HCoV-NL63 (~49%) and HCoV-229E (~48%)[1]. SARS-CoV-2 is even more closely related to coronaviruses identified in horseshoe bats, suggesting that horseshoe bats are the primary animal reservoir with a possible

and cell-mediated immunopathology (Box 1). ADE caused by enhanced viral replication has been observed for other viruses that infect macrophages, including dengue virus[13,14] and feline infectious peritonitis virus (FIPV)[15]. Furthermore, ADE and ERD has been reported for SARS-CoV and MERS-CoV both in vitro and in vivo. The extent to which ADE contributes to COVID-19 immunopathology is being actively investigated.

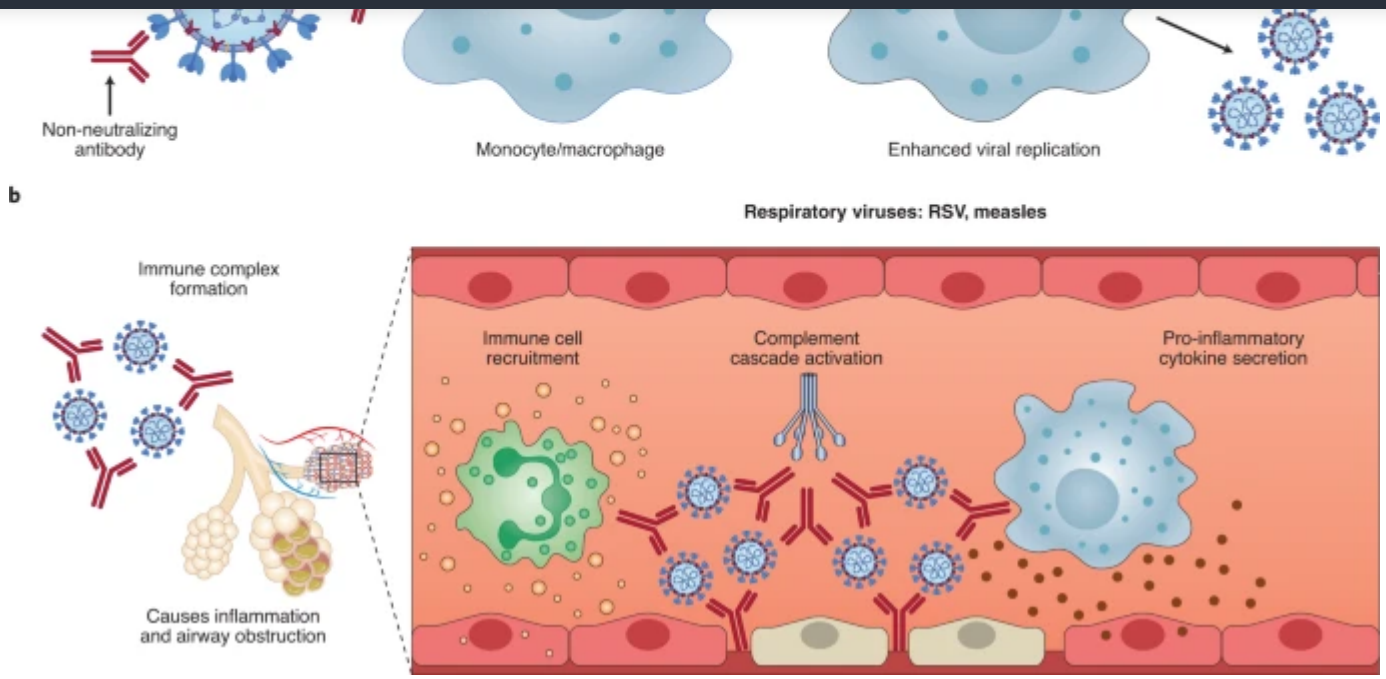
In this Perspective, we discuss the possible mechanisms of ADE in SARS-CoV-2 and outline several risk mitigation principles for vaccines and therapeutics. We also highlight which types of studies are likely to reveal the relevance of ADE in COVID-19 disease pathology and examine how the emerging data might influence clinical interventions.

## Box 1 ADE and ERD

ERD

in cats[16]. In this mechanism, non-neutralizing antibodies bind to the viral surface and traffic virions directly to macrophages, which then internalize the virions and become productively infected. Since many antibodies against different dengue serotypes are cross-reactive but non-neutralizing, secondary infections with heterologous strains can result in increased viral replication and more severe disease, leading to major safety risks as reported in a recent dengue vaccine trial[13,14]. In other vaccine studies, cats immunized against the FIPV S protein or passively infused with anti-FIPV antibodies had lower survival rates when challenged with FIPV compared to control groups[17]. Non-neutralizing antibodies, or antibodies at sub-neutralizing levels, enhanced entry into alveolar and peritoneal macrophages[18], which were thought to disseminate infection and worsen disease outcome[19].

**Fig. 1: Two main ADE mechanisms in viral disease.**



functions can enhance respiratory disease by initiating a powerful immune cascade that results in observable lung pathology[20,21]. Fc-mediated activation of local and circulating innate immune cells such as monocytes, macrophages, neutrophils, dendritic cells and natural killer cells can lead to dysregulated immune activation despite their potential effectiveness at clearing virus-infected cells and debris. For non-macrophage tropic respiratory viruses such as RSV and measles, non-neutralizing antibodies have been shown to induce ADE and ERD by forming immune complexes that deposit into airway tissues and activate cytokine and complement pathways, resulting in inflammation, airway obstruction and, in severe cases, leading to acute respiratory distress syndrome[10,11,22,23]. These prior observations of ADE with RSV and measles have many similarities to known COVID-19 clinical presentations. For example, over-activation of the complement cascade has been shown to contribute to inflammatory lung injury in COVID-19 and SARS[24,25]. Two recent studies found that S- and RBD-specific immunoglobulin G (IgG) antibodies in patients with COVID-19 have lower levels of fucosylation within their Fc domains[26,27]—a phenotype linked to higher affinity for FcγRIIIa, an activating Fc receptor (FcR) that mediates antibody-dependent cellular cytotoxicity. While this higher affinity can be beneficial in some cases via more vigorous FcγRIIIa-mediated effector

## Evidence of ADE in coronavirus infections in vitro

While ADE has been well documented in vitro for a number of viruses, including human immunodeficiency virus (HIV)[33,34], Ebola[35,36], influenza[37] and flaviviruses[38], the relevance of in vitro ADE for human coronaviruses remains less clear. Several studies have shown increased uptake of SARS-CoV and MERS-CoV virions into FcR-expressing monocytes or macrophages in vitro[32,39,40,41,42]. Yip et al. found enhanced uptake of SARS-CoV and S-expressing pseudoviruses into monocyte-derived macrophages mediated by FcγRIIa and anti-S serum antibodies[32]. Similarly, Wan et al. showed that a neutralizing monoclonal antibody (mAb) against the RBD of MERS-CoV increased the uptake of virions into macrophages and various cell lines transfected with FcγRIIa[39]. However, the fact that antigen-specific antibodies drive phagocytic uptake is unsurprising, as monocytes and macrophages can mediate antibody-dependent phagocytosis via FcγRIIa for viral clearance, including for influenza[43]. Importantly, macrophages in infected mice contributed to antibody-mediated clearance of SARS-CoV[44]. While MERS-CoV has been found to productively infect macrophages[45], SARS-CoV infection of macrophages is abortive and does not

tract more quickly, contradicting a simpler hypothesis that antibody titres are simply caused by higher viral loads. Other studies showed that anti-SARS-CoV-2 T-cell responses could be found at high levels in mild and asymptomatic infections[51,52]. Taken together, the data suggest that strong T-cell responses can be found in patients with a broad range of clinical presentations, whereas strong antibody titres are more closely linked to severe COVID-19. One important caveat is that viral shedding was measured in the upper respiratory tract rather than in the lower respiratory tract[50]. The lower respiratory tract is likely more important for severe COVID-19 lung pathology, and it is unclear how closely SARS-CoV-2 viral shedding in the upper and lower respiratory tracts correlate throughout the disease course.

Beyond the host response to new SARS-CoV-2 infections, the potential of pre-existing antibodies against other human coronavirus strains to mediate ADE in patients with COVID-19 is another possible concern[53]. Antibodies elicited by coronavirus strains endemic in human populations (such as HKU1, OC43, NL63 and 229E) could theoretically mediate ADE by facilitating cross-reactive recognition of SARS-CoV-2 in the absence of viral neutralization. Preliminary data show that antibodies from

were linked to Th2 cytokine biased responses[60] and/or excessive lung eosinophil infiltration[61]. Rational adjuvant selection ensures that Th1-cell-biased responses can markedly reduce these vaccine-associated ERD risks. Candidate SARS-CoV vaccines formulated with either alum, CpG or Advax (a delta inulin-based adjuvant) found that while the Th2-biased responses associated with alum drove lung eosinophilic immunopathology in mice, protection without immunopathology and a more balanced Th1/Th2 response were induced by Advax[62]. Hashem et al. showed that mice vaccinated with an adenovirus 5 viral vector expressing MERS-CoV S1 exhibited pulmonary pathology following viral challenge, despite conferring protection. Importantly, the inclusion of CD40L as a molecular adjuvant boosted Th1 responses and prevented the vaccine-related immunopathology[63].

Should it occur, ERD caused by human vaccines will first be observed in larger phase II and/or phase III efficacy trials that have sufficient infection events for statistical comparisons between the immunized and placebo control study arms. Safety profiles of COVID-19 vaccines should be closely monitored in real time during human efficacy trials, especially for vaccine modalities

antibodies that enhanced infection in vitro and resulted in more severe lung pathology in vivo[67].

In contrast, to determine whether low titres of neutralizing antibodies could enhance infection in vivo, Luo et al. challenged rhesus macaques with SARS-CoV nine weeks post-immunization with an inactivated vaccine, when neutralizing antibody titres had waned below protective levels[68]. While most immunized macaques became infected following viral challenge, they had lower viral titres compared to placebo controls and did not show higher levels of lung pathology. Similarly, Qin et al. showed that an inactivated SARS-CoV vaccine protected cynomolgus macaques from viral challenge and did not result in enhanced lung immunopathology, even in macaques with low neutralizing antibody titres[69]. A study in hamsters demonstrated that despite enhanced in vitro viral entry into B cells via FcγRII, animals vaccinated with the recombinant SARS-CoV S protein were protected and did not show enhanced lung pathology following viral challenge[70].

SARS-CoV immunization studies in animal models have thus produced results that vary greatly in terms of protective efficacy,

of enhanced pathology in rhesus macaques[74]. Going forward, increased vaccine studies in the Syrian hamster model may provide critical preclinical data, as the Syrian hamster appears to replicate human COVID-19 immunopathology more closely than rhesus macaque models[75].

## ADE and recombinant antibody interventions

The discovery of mAbs against the SARS-CoV-2 S protein is progressing rapidly. Recent advances in B-cell screening and antibody discovery have enabled the rapid isolation of potent SARS-CoV-2 neutralizing antibodies from convalescent human donors[76,77] and immunized animal models[78], and through re-engineering previously identified SARS-CoV antibodies[79]. Many more potently neutralizing antibodies will be identified in the coming weeks and months, and several human clinical trials are ongoing in July 2020. Human trials will comprise both prophylactic and therapeutic uses, both for single mAbs and cocktails.

results in the enhancement of disease and lung immunopathology. If ADE of neutralizing or non-neutralizing mAbs is a concern, the Fc portion of these antibodies could be engineered with mutations that abrogate FcR binding[80]. Animal studies can help to inform whether Fc-mediated effector functions are crucial in preventing, treating or worsening SARS-CoV-2 infection, in a similar way to previous studies of influenza A and B infection in mice[84,85] and simian-HIV infection in macaques[86,87]. An important caveat for testing human mAbs in animal models is that human antibody Fc regions may not interact with animal FcRs in the same way as human FcRs[88]. Whenever possible, antibodies used for preclinical ADE studies will require species-matched Fc regions to appropriately model Fc effector function.

## ADE and convalescent plasma interventions

Convalescent plasma (CP) therapy has been used to treat patients with severe disease during many viral outbreaks in the absence of effective antiviral therapeutics. It can offer a rapid solution for therapies until molecularly defined drug products can

established respiratory infection. As we highlighted above with recombinant mAbs, and as shown in historical dengue virus mother–infant data, the theoretical risk of ADE in CP prophylaxis is highest in the weeks following transfusion, when antibody serum neutralization titres fall to sub-protective levels. ADE risks in CP studies will be more difficult to quantify than in recombinant mAb studies because the precise CP composition varies widely across treated patients and treatment protocols, especially in CP studies that are performed as one-to-one patient–recipient protocols without plasma pooling.

To mitigate potential ADE risks in CP therapy and prophylaxis, plasma donors could be pre-screened for high neutralization titres. Anti-S or anti-RBD antibodies could also be purified from donated CP to enrich for neutralizing antibodies and to avoid the risks of ADE caused by non-neutralizing antibodies against other SARS-CoV-2 antigens. Passive infusion studies in animal models are helping to clarify CP risks in a well-controlled environment, both for prophylactic and therapeutic use. Key animal studies (especially in Syrian hamsters, and ideally with hamster-derived CP for matched antibody Fc regions) and human clinical

risks against intervention efficacy if clinical ADE is observed. Ongoing animal and human clinical studies will provide important insights into the mechanisms of ADE in COVID-19. Such evidence is sorely needed to ensure product safety in the large-scale medical interventions that are likely required to reduce the global burden of COVID-19.

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## Acknowledgements

**ARC Centre for Excellence in Convergent Bio-Nano Science and Technology, University of Melbourne, Parkville, Victoria, Australia**

Adam K. Wheatley & Stephen J. Kent

**Melbourne Sexual Health Centre and Department of Infectious Diseases, Alfred Hospital and Central Clinical School, Monash University, Melbourne, Victoria, Australia**

Stephen J. Kent

**Department of Pharmaceutical Chemistry, The University of Kansas, Lawrence, KS, USA**

Brandon J. DeKosky

**Department of Chemical Engineering, The University of Kansas, Lawrence, KS, USA**

Brandon J. DeKosky

## Competing interests

The authors declare no competing interests.

## Additional information

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16 May 2020

Accepted

20 August 2020

Published

09 September 2020

Issue Date

October 2020

DOI

https://doi.org/10.1038/s41564-020-00789-5

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