Some notes by Jesse Bloom on papers related to coronavirus ADE

Antibody-dependent enhancment of Coronavirus infection

- Antibody responses against SARS coronavirus are correlated with disease outcome of infected individuals: Generate lentiviral particles pseudotyped with SARS-CoV Spike (note that they have to codon optimize Spike). Show that it best infects 293T-ACE2 cells, and also Vero pretty well. Then looks at the kinetics of neutralizing anti-Spike antibodies in deceased versus recovered patients. There seem to be so many confounders in this study that I'm not sure what can be concluded. But both sets of patients developed neutralizing antibody responses, although they often appear to wane after about 20 days in the deceased patients. Overall the responses look pretty similar to me between groups, although paper says that recovered patients had higher responses.

- Anti-SARS-CoV IgG response in relation to disease severity of severe acute respiratory syndrome: Compares IgG levels at various timepoints in patients with SARS. Reports patients with more severe disease had higher earlier IgG, although the effect looks pretty marginal to me. I would also think there significant potential confounders, such as higher viral titer being correlated with both disease and antibody response, exact initial time of infection unknown, etc. This paper appears to be one of the bases of the suggestion that there is ADE.

- Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients: Describes giving convalescent sera to SARS patients. Administration of this sera prior to day 16 was associated with better outcomes than administration of a steroid, although it's not a controlled study.

- Use of convalescent plasma therapy in SARS patients in Hong Kong: Administered convalescent sera to SARS patients. Early administration of this sera (prior to day 14) was associated with better outcomes, and authors speculate outcomes are better if viremia still high at time of transfer. Although it's not a controlled study.

- Evaluation of Antibody-Dependent Enhancement of SARS-CoV Infection in Rhesus Macaques Immunized with an Inactivated SARS-CoV Vaccine: Vaccinated macaques with inactivated SARS-CoV vaccine, trying to vaccinate so as to only elicit low levels of neutralizing antibodies (reciprocal dilution of 10 after 9 weeks). The animals were then challenged with SARS-CoV. The vaccination was clearly not sterilizing, as it only slightly reduced viral titers at day 2 and a bit more at day 5 and 7. However, the animals were much better protected against disease by the vaccine. So no evidence of ADE here.

- Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins: Shows that infection of the HL-CZ cell line by SARS-CoV is enhanced by

1000-fold dilutions of anti-sera from patients, but inhibited by 10-fold dilutions. They also use mouse serum to confirm that it's antibodies against Spike that have the effects. There is also some data using monoclonal antibodies although these antibodies are described so poorly that it's hard to draw conclusions. Overall, shows ADE in some regimes in cell culture. Importantly, this is ADE at the level of enhanced entry into a cell line, not disease.

- Monoclonal antibodies to the spike protein of feline infectious peritonitis virus mediate antibody-dependent enhancement of infection of feline macrophages: Describes other papers about how cats infected with the coronavirus feline infectious peritonitis virus (FIPV) have more disease if they are seropositive, and how transfer of immune sera can enhance disease. Shows that at sera dilutions of 1:2000, infection can be enhanced by 56-fold in macrophages. Then showed 12 of 37 antibodies to Spike could enhance infection, and most of these antibodies were also neutralizing in a non-macrophage cell line. It does seem clear that there is ADE in cats with FIPV.

- Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV challenge despite their capacity to mediate FcgammaRII-dependent entry into B cells in vitro: Vaccinated mice and hamsters with trimeric Spike; although a single injection produced low antibody titers, sequential (2 or 3) induced high levels. An alum adjuvant slightly improved titers, and made them much more durable. The neutralizing titers were around 1:5000. The neutralizing antibodies appeared to block interaction with ACE2. At around 1:1000 dilutions, the sera enhanced viral entry into B cells expressing Fc receptor. Shows that immunized hamsters are mostly protected against disease.

- Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry: Examines antibody-dependent enhancement and neutralization of SARS-CoV and MERS-CoV using antibodies 33G4 and Mersmab, respectively. Both antibodies neutralize the viruses in cells expressing normal receptors (ACE2 or DPP4), but somewhat increase infection in cells expressing Fc receptors. They then show that binding to the receptor (DPP4) or the antibody allows MERS-CoV Spike to be cleaved by trypsin at S2' as well as S1/S2, in the absence it is only cleaved at S1/S2. When cells have both DPP4 and Fc receptor, there is a balance and low antibody concentrations aid infection.

- Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS: Shows that antibodies can potentiate infection of human immune cells including monocytes and macrophages by SARS-CoV. But at least in macrophages (the only ones examined), the viral infection does not produce progeny and doesn't change gene expression profile.

- Is COVID-19 receiving ADE from other coronaviruses?: A wildly speculative perspective piece that argues that perhaps ADE due to priming with other coronaviruses explains with COVID-19 is worse in Hubei. No data, and cites a variety of other papers out of context, conflating studies showing enhanced infection of immune cells at low antibody dilutions with actual disease ADE.

- Evasion of antibody neutralization in emerging severe acute respiratory syndrome coronaviruses: Performs neutralization assays of SARS Spike pseudotyped lentiviral vectors with purified IgG from several vaccine candidates. Looks at several SARS Spikes (such as Urbani) and some civet ones. For most SARS Spikes, anti-SARS mouse IgG neutralizes entry (although it does not for one later SARS strain, GD03T0013). The civet CoV Spikes, the IgG actually enhances entry in cell culture. Transplanting the human ACE-2 binding residues into civet makes it neutralization sensitive, and transplanting the civet into the human makes it neutralization resistant. However, a hugely important point appears to be Fig 3b, which shows that the lack of human ACE-2 binding residues makes the virsu orders of magnitude less infectioius overall. So it seems possible that real efficient infection requires ACE2 binding, which is well inhibited. But viruses that don't bind ACE-2 have low level infection which is enhanced by IgG–but the infection remains poor in absolute terms, something that is obscured by the fact that most figures plot percent neutralization.

- Neutralizing Antibody Response and SARS Severity: Examines antibody levels and disease severity in SARS patients. They find that patients with severe disease tend to have higher neutralizing antibody responses. But they conclude that this could be due to confounders like higher viral load also leading to more antibody, and write "our finding that high neutralizing antibody correlating with clinical severity should not be interpreted to mean that neutralizing antibody is harmful."

- Immunodominant SARS Coronavirus Epitopes in Humans Elicited both Enhancing and Neutralizing Effects on Infection in Non-human Primates: Looks at ADE in macaques. Lots of in vitro data looking at enhanced cell entry with antibodies / sera. Then infects macaques given peptide vaccines. Table 2 appears to show 2 of 3 vaccines strongly protect versus control group (Vac 1), whereas other vaccine has no real effect. Then infects macaques given high levels of an mAb pre-infection, and shows at level of histology things are worse with the antibody. This definitely shows there can be enhancing effect. But I can't help but feel that the paper is written to "drum up" the ADE aspect rather than the main finding that despite peptide vaccines probably not being a great approach, most of the vaccines protect against disease.

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