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Can antigenic drift of SARS-CoV-2 spike protein jeopardize current vaccine development?

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Introduction

An effective vaccine against COVID-19 is widely considered the most promising exit strategy from the gravest pandemic in over a century. There were over 70 candidates employing diverse technology platforms as reported by the WHO in April 2020, most targeting the spike (S) protein/subunits of SARS-CoV-21.

Evidence for SARS-CoV-2 Antigenic Drift

Early sequencing efforts from the epicenter of pandemic in Wuhan, China revealed >99% similarity among virus isolates from an index cohort of patients; this supports the single-source of origin through a zoonotic event (thought to be from bats via an intermediate host) followed by rapid human-to-human transmission2,3. However, subsequent analysis of SARS-CoV-2 genomics data from around the world has discovered evidence of in human clonal evolution with concerning implications for ongoing vaccine development efforts. Forster et al. utilized phylogenetic network analysis on a limited dataset from the international Global Initiative on Sharing Avian Influenza Data (GISAID) to discover at least three central variants (A, B, C) that are distinguished by amino acid changes and apparently occupied unique geographies in early stages of the pandemic4. A word of caution is the appropriateness of this reported use of median-joining network (MJN) analysis and its Steinerization process to investigate the phylogenetics of a novel virus based on limited genomics data prone to sampling bias5,6. As such, any inference specifically of SARS-CoV-2 evolutionary directionality will need to be tempered for now.

In a similar vein though, Farkas et al. demonstrated point mutational signatures (majority missense variants) with founder patterns of transmission within geographical clusters, indicating continued evolution as the pandemic unfolded7. A noteworthy observation from this study was the higher frequency of mutations affecting the helicase and ORF1ab proteins of SARS-CoV-2 compared to structural proteins. This suggests the actively evolving regions of the virus genome predominantly encode the non-structural proteins, a notion that has more implications for continuous design of RT-qPCR primer sets for diagnosis.

However, a recent preprint of a larger analysis from an international collaboration further suggests positive selection of S mutant forms of the virus8. In particular, the G clade harboring the D614G mutation of S protein is seemingly increasing in frequency across geographical regions. While claims of higher transmissibility need functional validation, it has evidently become the dominant form in much of Europe after introduction in early February 2020.

Implications for Investigational Vaccine Candidates

A case in point is the Phase I/II clinical trial by University of Oxford with the candidate vaccine ChAdOx1 nCoV-19 under

investigation compared to the approved meningococcal vaccine MenACWY as a control (ClinicalTrials.gov Identifier: NCT04324606). This particular immunogen utilizes a well-studied, relatively safe chimpanzee attenuated adenovirus vector (ChAdOx1) displaying the S protein on its surface. The vaccine construct may generate high cellular and humoral immune responses against the S protein in a vaccinated individual, thus potentially conferring immunity to COVID-19. However, sequence for this epitope just like most other immunogens is based on the index variant 'WH-Human1' genome reported from Wuhan, China. Therefore, it may not be assumed antibodies thus generated will have cross-neutralizing capabilities against these new mutants reported by Korber et al.

Indeed, published data suggest that convalescent-phase plasma from most patients recovered from COVID-19 do not contain high levels of receptor binding domain (RBD)-specific antibodies9. With only a minority (1%) of convalescent individuals mounting highly neutralizing titers above 1:5,000 in the study by Robbiani et al., this can leave the majority naïve or partially immune against SARS-CoV-2 if non-specific S protein constructs are employed for vaccination. In fact, this polyclonal nature of the host antibody response may in part explain the wide clinical spectrum of disease from asymptomatic to fatal presentations that have characterized COVID-19. Farrera et al. in a preprint also demonstrate the importance of specific antibodies against immunodominant linear epitopes corresponding to key proteolytic sites responsible for 'priming the spike' in convalescent patients10. Intriguingly, the bottom part of the coronavirus S protein facilitating cellular fusion as opposed to the top part, the latter having received the bulk of attention as an antibody target, can be a more promising target for antibody-dependent neutralization.

So can antigenic drift of SARS-CoV-2 spike protein jeopardize current vaccine development? While some of these observations are preliminary requiring validation, concerns should be raised now for early modification if feasible of current COVID-19 vaccine trials such as the Oxford initiative to address evolutionary transitions of SARS-CoV-2. Vaccine development is already fraught with attrition rates of >90%1; as such, ongoing reconstitution of vaccine constructs may be imperative to both reflect the prevalence of emerging viral mutants and avert ultimate clinical failure. The optimal strategy may be design and/or re-design of immunogens regardless of the platform utilized to elicit neutralizing antibodies against specific epitopes (tentatively identified) of the RBD, thereby enhancing the quality and duration of the host immune response.

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