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Publication Date

2021-04-01

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Acknowledgements

This work is supported by the Health Sciences and Public Health Division of the Undergraduate Laboratory at Berkeley (ULAB) at the University of California, Berkeley. This paper is under leadership, assistance, and research management of undergraduate research mentors, Rebecca Shuere. Research director Angikaar Chana and other ULAB board members are responsible for the development and production of this paper.

Abstract

This is a literature review on the effects of spike mutations in the B1.1.7 SARS-CoV-2 variant and its effect on vaccine efficacy. This paper has organized the pertinent literature on the researched effects of vaccine efficacy and explores a number of mutations in the spike protein. The search was conducted on PubMed and the criteria for inclusion was based on relevance to specifically mutations in the B1.1.7 variant, being a primary source, conducted after January of 2021, and its reproducibility and pertinence to the research topic. There are 16 fully extracted studies discussed in the results, with a brief overview of the conducted experiment in relation to the papers' conclusions. The strengths of this paper are distilling the molecular methods of these individual papers and being able to compare and contrast diverse experiments on the same mutations. However, due to the diversity of experiments discussed in this paper, the landscape of SARS-CoV-2 mutations and vaccine efficacy are difficult to distill. The discussed papers were evaluated on the possible threats of the mutations and the comparable effect of known mutations. This is an important step for evaluating transmissibility and virulence. This literature review further shows the need to have a standard set of experiments that can be used to evaluate the effect of mutations in SARS-CoV-2 variants and its effect on vaccine efficacy in order to make

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the cause of global COVID-19 pandemic. There are four major structural components encoded by the viral genomes, including nucleoprotein, spike proteins, envelope proteins and the membrane proteins (Rathnasinghe et al.). The spike protein responsible for the entry of human host cells via binding receptor angiotensin-converting enzyme2 (ACE2), which allowed it to be the major target for the

development of vaccination and other therapeutic antibody interventions (Diamond et al.), such as nucleoside-modified mRNA-LNP vaccine mentioned in Weissman, Drew et al. and various spike protein mutants demonstrated different levels of neutralization titers in immune response (Weissman, Drew et al.).

Previous studies indicated that newly emerging SARS-CoV-2 variants which included the U.K. (B1.1.7 lineage), South Africa (B.1.351), Brazil (B.1.1.248), have substitutions on the spike proteins such as N501Y, and D614, which might resist the newly generated antibody and the effect of the vaccine (Diamond et al.). SARS-CoV-2, similar to all viruses, is subject to mutations that may influence the fitness and subsequent transmissibility of the resultant variants. One such evolutionary lineage under consideration of high risk is the B.1.1.7, originally detected in the UK and thereafter spreading to a global scale (Volz et al.). The spread and dominance of this variant line warrants investigation into the possibility of selective advantages and the potential need to alter vaccines to safeguard against them. The scale and points of interest of these investigations span a great breadth. One such consideration lies in binding capabilities of the virus with human cells, with research focused on the human ACE2 receptor--the primary binding site for SARS-CoV-2. Mutations may impact binding efficiency as the mutations on spike proteins may yield higher affinity to the binding sites of the ACE2 receptor, yielding stronger bonds and greater rates of entry into human host cells.

From the perspective of public health concern, accompanying morbidity and mortality, there is a need to identify mutations that may lower the efficacy of vaccines, especially with ongoing efforts to reach herd immunity. As existing evidence indicates that SARS-CoV-2 also disproportionately impacts the life qualities of specific populations, such as elderly and people with chronic diseases like obesity and Type 2 diabetes mellitus,(Rathnasinghe, Raveen, et

al.2021). Additionally, there is literature suggesting effects of mutations on transmissibility through alterations of binding efficiency, often expressed with measures of higher viral loads among these mutated variants (Daniloski et.al). The continual mutation and proliferation of the SARS-CoV-2 virus presents a concern for the long-lived efficacy of vaccines along with the potential for severity variance.

Methodology

Defining Search Terms and Inclusion Criteria

Search criteria were identified based on their relevance to the following question this paper attempts to address: How is the efficacy of SARS-CoV-2 vaccines affected by spike protein mutations in the B1.1.7 lineage? Accordingly, search terms such as “coronavirus spike protein”, “spike protein mutation”, “coronavirus vaccine”, “B1.1.7 lineage”, “U.K. variant”, “D614G”, “N5017”, “K417N”, and “E484K” were utilized. We conducted searches using one or more of these keywords on data search engines like PubMED and Google Scholar to survey existing studies. From the resulting papers, the criteria for selecting papers for our study were as follows: the study must have been conducted between January 2020 and April 2021 in order to ensure that it is relevant to current SARS-CoV-2 vaccination research, and it must be peer reviewed and published by an academic journal. To ensure that only primary scientific literature was included, papers that discussed only secondary information such as systematic reviews, literature reviews, and meta-analyses were excluded. Studies that met the inclusion criteria were selected if they were pertinent to the effects of spike protein mutations on vaccine efficacy and if they had sufficient information on methodology so as to be reproducible. In total, eighteen papers were selected by the described methodology.

Data Extraction

We categorized selected papers on the basis of several factors: study design (the categories were prospective cohort, cross sectional, case-control, nested case-control, retrospective cohort, or other), the spike protein mutation tested (including D614G, G614, K417N, E484K, and N501Y), presence of a negative control group and blinding, presence of confounding factors, addition of antibiotic in agar used for cell culture, primary statistical analysis methods, independent and dependent variables, etc. Data extraction was performed on a Google Sheets spreadsheet, where all papers were assigned numerical values corresponding to the categories they were sorted into for each of the mentioned criteria. We utilized the data extraction to identify broader trends between categories. Studies investigating the D614G variant tended to find that the threat presented by this variant to vaccine efficacy is negligible as observed in human, mouse, golden hamster, and Rhesus macaque models. Those evaluating E484K mutation tended to observe a reduction in neutralizing activity of vaccine-elicited and monoclonal antibodies against pseudoviruses with mutated E484K. Amongst the studies assessing the impact of the N501Y mutation, the general consensus was that human convalescent and post-vaccination sera had reduced neutralizing activity against pseudoviruses with mutated N501Y, especially when present along with D614G, E484K, and K417N mutations.

Results

Here, we briefly outline findings of the selected papers. “Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies,” by Chen et al. showed that adjustment to the spike sequences of vaccines may be needed to neutralize B1.1.7 viruses with the E484K spike mutation; they reported the effects of a panel of SARS-CoV-2 variants on antibody neutralization using monoclonal antibodies (mAbs) and human

convalescent and post-vaccination sera, and "many highly neutralizing mAbs...and most convalescent sera and [BNT162b2] vaccine-induced immune sera showed reduced inhibitory activity against viruses containing E484K" (Chen et al.). Collier et al. drew a similar conclusion: "Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies," demonstrated that E484K threatens BNT162b2 vaccine effectiveness, as in sera from BNT162b2 vaccinated volunteers, 19 of 31 mAbs had higher IC50 values and therefore lower neutralizing activity against B1.1.7 SARS-CoV-2 with E484K than without (Collier et al.). Other mutants like N501Y are also addressed in the article "The new SARS-CoV-2 strain shows a stronger binding affinity to ACE2 due to N501Y mutant," which demonstrated a potential mechanism responsible for N501Y variant transmissibility differences. The N501Y variant demonstrated a higher affinity for human ACE2 observed through the shorter atomic distances between the two. This effect is a result of changes in electrostatic interactions reducing the repulsive forces present between the N501Y bonding site and human ACE2. "Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera" written by Xie and colleagues analyzed three engineered SAR-CoV-2 mutants and their neutralization in vaccine-elicited sera. The results demonstrated different neutralization GMTs (geometric mean titers) from the parental virus for all variants, indicating small effects on neutralization by sera elicited by vaccinations. However, these variations were quite small in comparison to the criteria typically used when dictating a potential need for a strain change in influenza vaccines. In "mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants," neutralization assays showed that a cohort of BNT162b2 or mRNA-1273 vaccinated volunteers had reduced plasma neutralizing activity against SARS-CoV-2 variants containing E484K, N501Y, and K417N/E484K/N501Y, and 14 of 17 tested mAbs had increased IC50 values, or reduced

neutralization, against variants with the K417N, E484K and N501Y mutations (Wang et al.). In "Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity," neutralization potency of BNT162b2 and mRNA-1273 vaccinated individuals against 10 global SARS-Cov-2 variants was tested. 5 of 10 variants, containing some combination of K417N/T, E484K, and N501Y, had significantly higher PNT50 (pseudovirus neutralization) values relative to the wild-type (Garcia-Beltran et al.). Most notably, B1.1.7 did not have a significantly higher PNT50 value. Meanwhile, Hoffman and Plante's studies led to more questions about how mutations on spike protein can contribute to the host-virus interaction in the immune response. In "SARS-CoV-2 variants B.1.351 and P.1 escape from neutralizing antibodies," Hoffman et al. demonstrated that the entry of the B.1.351 could be partially or fully resistant to the antibody treatments, indicating that SAR-CoV-2 might exist certain unknown mechanisms to facilitate them to escape the antibody neutralization in host immune system. "Spike mutation D614G alters SARS-CoV-2 fitness and neutralization susceptibility," pointed out that the spike D614G mutation enhanced viral replications via increased virion infectivity in the upper tract (Plante et al.). Furthermore, Weissman, Drew et al. focused on the function of nucleoside-modified mRNA-LNP vaccine, and compared the vaccinated mice, Rhesus macaques, and convalescent serum samples from people known to be infected with either the D614 or G614 variant using vaccine platform encoding four different SARS-CoV-2 spike immunogens that generated antibody responses. The results indicated that the G614 mutation had stronger titers of neutralization to this virus variant compared to D614G variant (Weissman, Drew et al.). Meanwhile, Baum, Alina, et al. pointed out that anti-SARS-CoV2 spike mAbs demonstrated broad neutralization across SARS-CoV-2 spike RBD (receptor binding domain) variants. Sequencing of escape mutants revealed that single amino acid changes can ablate binding even to

antibodies that were selected for breadth against all known RBD variants. They also proposed that antibody cocktail therapy provided a powerful way to minimize mutational escape by SARS-CoV-2 in comparison to a single antibody treatment; in particular, their studies point to the potential value of antibody cocktails in which two antibodies were chosen so as to bind to distinct and non-overlapping regions of the viral target (in this case, the RBD of the spike protein), and thus require the unlikely occurrence of simultaneous mutations at two distinct genetic sites for viral escape, improving drug efficacy (Baum, Alina, et al.).

Regarding the differences between D614G and G614 mutants at the genomic level, the article by Volz and colleagues entitled “Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity” unveiled inconclusive trends indicating selective advantage for the G614 spike mutation variant compared to the wild type D614 when analyzing logistic growth models. However, correlation was determined between the G614 variant and higher viral loads and a younger age distribution. The findings are limited in scope due to extreme noise in population-driven data and limitations in accounting for demographic processes. “Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus” by Korber et. al. also demonstrates these findings. The G614 strain was found in increasing frequency when compared to D614 while cocirculating, suggesting possible positive selection. Furthermore, the study found G614 to be associated with higher viral nucleic acid in the upper respiratory tract in humans, which suggests higher viral loads and higher infectivity in multiple pseudotyping assays. Similarly, "The G614 pandemic SARS-CoV-2 variant is not more pathogenic than the original D614 form in adult Syrian hamsters" explored the potential virality and transmissibility of the G614 variant in Syrian hamsters. Using viral load in nasal wash samples, analysis of lung histopathology, and records of

body mass loss over the course of infection, Stauft and colleagues found no significant variance between the G614 and D614G variants. The data did suggest potential growth advantage, but such advantage was disjoint from overall pathogenicity. From the cellular level, Daniloski and colleagues explore human cell interactions in their article, "The Spike D614G mutation increases SARS-CoV-2 infection of multiple human cell types." They discovered that in samples composed of human cell lines derived from the liver, lung, and colon, the SARS-COV-2 G614 pseudotyped lentivirus transduced more cells (~1.5 to ~8 times more) after infection in comparison to the D614G alternative. An observed resistance to cleavage in the G614 variant suggested a potential mechanism propagating the increased transduction potential. Meanwhile, in "D614G Mutation Alters SARS-CoV-2 Spike Conformation and Enhances Protease Cleavage at the S1/S2 Junction" Gobeil and colleagues further investigate the potential mechanism behind the higher transmissibility of the G614 variant over D614G. The G614 variant was observed to have an altered RBD with structural changes consistent with higher furin cleavage efficiency. The higher cleavage efficiency was suggested to be a potential source of the G614 increased viral load.

Discussion

Limitations and Future Investigations

Several limitations are present in the selected studies. For example, Hoffman et al. stimulated the cell entry model of SARS-CoV-2 via using VSV pseudotyped with only the S proteins of SARS-CoV-2 variant. They also pointed out that the experiments conducted in the immortalized cell lines should be replicated to primary cell lines (Hoffmann et al.). Hoffmann et al. did succeed in accounting for other cell-surface proteins that may play a role in natural infection such as TMPRSS2, which Garcia-Beltran et al. failed to account for; they utilized an in

vitro neutralization assay with engineered 293T-ACE2 target cells that "restrict pseudovirus entry in an ACE2-dependent manner and lack other cell-surface proteins" (Garcia-Beltran et al.). A key limitation of Wang et al. is the use of single mutations or combinations of spike mutations that do not naturally occur in B1.1.7.

Both Chen et al. and Baum et al. proposed that antibody cocktail therapy is a potential approach to minimize the escape of SARS-CoV-2 mutants. Further investigation into the use of multiple antibodies in conjunction would allow us to better target the RBD of the spike protein, especially the distinct and non-overlapping sites. Garcia-Beltran et al. also suggest additional studies to evaluate the role played by cellular immune responses mediated by T cells and NK cells in response to BNT162b2 and mRNA-1273 vaccination, which "are likely to play a key role in disease prevention for vaccine recipients" (Garcia-Beltran at al.).

A key limitation of our study is that not every paper that fit the search criteria was included. The selected studies were chosen based on pertinence to the effects of spike protein mutations on vaccine efficacy and if they had sufficient information on methodology so as to be reproducible. However, there is no quantitative scale to measure reproducibility or pertinence, this was instead discussed in a journal club and had to be voted reproducible and pertinent in order to extract results.

Overarching Trends

All five studies that addressed the effect of the E484K spike mutation noted its potential to threaten neutralization potency of humoral immune responses induced by human convalescent sera and sera from BNT162b2 and mRNA-1273 vaccinated individuals (Chen et al.; Collier et al.; Wang et al.; Xie et al.; Garcia-Beltran et al.). Reduction of neutralizing activity was observed in a variety of engineered pseudoviruses in the five studies, but Collier et al. evaluated the impact

of E484K in a B1.1.7 context and they warn that introduction of E484K in a B1.1.7 background could significantly lower neutralization of monoclonal antibodies that target the RBD and RBM (receptor binding motif), even in BNT162b2-vaccinated individuals. Collier et al. showed that more vaccine-elicited and monoclonal antibodies tested had significant loss of neutralization potency when the E484K mutation was introduced in B1.1.7 than when it was not introduced. Chen et al. similarly demonstrated that 4 antibodies that targeted the RBM had virtually complete loss of neutralizing activity against pseudoviruses containing the E484K mutation, and they suggest that the E484K mutation has prompted the need for "updated mAb cocktails targeting highly conserved regions, enhancement of mAb potency or adjustments to the spike sequences of vaccines may be needed to prevent loss of protection in vivo" (Chen et al.). It is vital that measures are implemented to adjust antibody cocktails and vaccinations against the E484K spike mutation.

Amongst the studies that assessed the effect of the N501Y spike mutation in a B1.1.7 context, the general consensus is that it reduces vaccine efficacy when present in conjunction with other specific RBD mutations but also has the potential to reduce neutralizing activity on its own. Xie et al. demonstrated that the ratio of neutralizing titers from BNT162b2-vaccinated sera against mutant N501Y, Δ69/70 + N501Y + D614G and E484K + N501Y + D614G viruses to their titers against the USA-WA1/2020 virus were 1.46, 1.41 and 0.81 respectively; only the E484K + N501Y + D614G pseudovirus had lower neutralizing titres from post-vaccination sera. Chen et al. similarly found that the mutant E484K + N501Y + D614G virus had the most antibodies with EC50 (potency) values greater than 10,000. However, Wang et al. also showed that the pseudovirus with mutant N501Y alone had higher IC50 values than the wild-type for all 17 antibodies tested. Ali et al. provide evidence that this inhibitory activity is partially a result of

the binding affinity of SARS-CoV-2 to human ACE2, which is higher in the N501Y mutated structure than that in the wild-type due to a change in electrostatic interactions. The N501Y mutation, both when alone in engineered pseudoviruses and when present along with other RBD mutations in a B1.1.7 background, presents a threat to BNT162b2 vaccine efficacy and the neutralizing activity of several RBD-targeting antibodies.

Regarding the effect of D614G, seven papers suggest that the threat presented by this variant to vaccine efficacy is negligible (Papers 5, 8, 10, 11, 12, 13, 15). Despite presenting higher viral loads in almost all circumstances, functioning as a proxy for increased transmissibility, the D614G variant does not appear to possess any attributes making it more resistant to neutralization. In fact, Paper 10 goes so far as to indicate this variant being more susceptible to vaccination efforts. This is especially interesting when considering the D614G variant is considered to have a higher fitness, having superseded the original virus in frequency shortly after its initial documented appearance.

Conclusion

From the data we analyzed from the selected papers, the results suggest that the antibodies generated by the current vaccines can neutralize the B1.1.7 variant of SARS-CoV-2 but with decreased efficiency under a cohort of the spike protein mutation tested (including D614G, G614, K417N, E484K, and N501Y), which was demonstrated in both mice and human experimental objectives. There are a couple of ongoing hypotheses that could explain the differences in vaccination efficiency; one being that the spike mutation enhances viral replications via increased virion infectivity in the upper respiratory tract. Also, the studies on the escape of mutants from neutralization in immune response can lead to various potential treatments such as “antibody cocktail” therapies. With new mutations rapidly emerging, further

studies need to be conducted on the effects of changes in the spike protein of SARS-CoV-2 virus on the efficacy of vaccines.

Assigned Number	Study (Author, Title)
1	Ali, Fedaa et al. “The new SARS-CoV-2 strain shows a stronger binding affinity to ACE2 due to N501Y mutant.”
2	Baum, Alina et al. “Antibody Cocktail to SARS-CoV-2 Spike Protein Prevents Rapid Mutational Escape Seen with Individual Antibodies.”
3	Chen, Rite E. et al. “Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies.”
4	Collier, Dami A. et al. “Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies.”
5	Daniloski, Zharko et al. “The Spike D614G mutation increases SARS-CoV-2 infection of multiple human cell types.”
6	Diamond, Michael, et al. “SARS-CoV-2 Variants Show Resistance to Neutralization by Many Monoclonal and Serum-Derived Polyclonal Antibodies.”
7	Garcia-Beltran, Wilfredo F. et al. “Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity.”
8	Gobeil, Sophie M. et al. “D614G Mutation Alters SARS-CoV-2 Spike Conformation and Enhances Protease Cleavage at the S1/S2 Junction.”
9	Hoffmann, Markus, et al. “SARS-CoV-2 Variants B.1.351 and B.1.1.248: Escape from Therapeutic Antibodies and Antibodies Induced by Infection and Vaccination.”
10	Plante, Jessica A., et al. “Spike Mutation D614G Alters SARS-CoV-2 Fitness.”
11	Korber, Bette et al. “Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus.”
12	Stauft, Charles B., et al. “The G614 Pandemic SARS-CoV-2 Variant Is Not More Pathogenic than the Original D614 Form in Adult Syrian Hamsters.”

13	Volz, Erik et al. “Evaluating the Effects of SARS-CoV-2 Spike Mutation D614G on Transmissibility and Pathogenicity.”
14	Wang, Zijun et al. “mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants.”
15	Weissman, Drew et al. “D614G Spike Mutation Increases SARS CoV-2 Susceptibility to Neutralization.”
16	Xie, Xuping et al. “Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera.”

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