Commentary

SARS-CoV-2 variants: Subversion of antibody response and predicted impact on T cell recognition

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COVID-19 variants of concern, including B.1.1.7, B.1.351, and P.1, encompass mutations facilitating immune evasion. Neutralizing antibody recognition and function may be variably impaired. We considered the impact of mutations on T cell responses. Mutations could be neutral or result in either loss or gain of predicted epitopes depending on HLA type.

There have been recent descriptions of an increasingly prevalent SARS-CoV-2 variant phylogenetic cluster and, notably, the B.1.1.7 lineage (sometimes termed VOC 202012/01), which is associated with increased transmission in the United Kingdom. This variant is now described in some 25 countries, as well as additional variants of concern identified in South Africa (B.1.351/501Y.V2) and Brazil (P.1).[1–4] B.1.1.7 encompasses coding mutations from the wild-type sequence.[1,2] With respect to the spike antigen, attention has been drawn to the impact of the N501Y mutation, one of the receptor binding domain (RBD) contact residues known to affect ACE2 binding, the P681H mutation adjacent to the furin-cleavage site, and the 69–70 deletion that ablates one of the neutralizing antibody binding epitopes. In addition, there are coding mutations within nucleocapsid (N), ORF1a and ORF8 (Data S1). Datasets are documenting the disproportionate spread of B.1.1.7 and related sequences, with modeling suggesting an increase in infectivity.[2] Implicated mechanisms rest largely on the notion of improved binding to ACE2 and increased viral load in nasopharyngeal samples.[5]

There has been concern and speculation about the possibility that some of these mutations may facilitate immune evasion, with implications both for risk of reinfection in those previously infected with the wild-type virus and for the risk of escape from immunity elicited by the first-generation spike vaccines.

Detailed mapping is available for the spike epitopes targeted by neutralizing antibodies.[4–6] It had been assumed from modeling that while the epitope centered on spike 69–70 is lost, overall, the neutralizing repertoire would be largely intact, with other neutralizing epitopes unaffected.[6–9] Preprints are now appearing in which the impact either of individual mutations or of the collective mutations within B.1.1.7, the South African 501Y.V2 or Brazilian B.1.1.28 and P.1 variants, is evaluated with respect to neutralization by convalescent sera (after natural infection with the wild-type variant), vaccinee sera after two boosts, or monoclonal antibodies generated from these immune repertoires.[3,4,] A report from Pfizer indicates marginal deleterious impact of the B.1.1.7 mutations on neutralization.[10] However, reports on neutralization of the other variants suggest a significant ablation of spike recognition.[3,4] In the study from Wang and colleagues, a quarter of their neutralizing monoclonal panel showed substantially reduced binding to at least one of the mutant RBDs.[3]

Analysis of the impact on T cell recognition is still in progress. The contribution to protective immunity from T cells, with CD4 Th1 immunity having been highlighted in the response to SARS-CoV-2, is broad, targeting epitopes spanning the viral proteome. Hundreds of proposed epitopes have now been described (though in most cases, without defined HLA restriction), these of varying fre-

quency within a given, infected individual and of varying prevalence as shared ("public") epitopes between individuals—those that can bind promiscuously within the peptide-binding grooves of diverse HLA alleles, with several such epitopes having been described.[11–14]

We considered the maximal potential impact on the CD4 T cell SARS-CoV-2 repertoire initially by mapping each of the B.1.1.7 and 501Y.V2 coding changes and asking whether these impinged on predicted epitopes (Tables S1A and S1D). In doing so, we note the caveat that predictive algorithms such as NetMHCIIpan have proven value in prediction of T cell epitopes, but a prediction of "strong binding" need not necessarily equate to a strongly stimulatory T cell epitope. Furthermore, because of the greater variation in peptide lengths, the predictive algorithms are somewhat less robust for HLAII than for HLAI. We focused on common HLA-DRB1 alleles in countries currently encountering the spread of B.1.1.7: HLA-DRB1*0101, 0301, 0401, 0701, 1101, 1301, and 1501. Nucleocapsid is epitope rich and, in most analyses, accounts for as great a component of the overall T cell response as spike. The B.1.1.7 mutation D3L is not predicted to lie within an epitope, and the S235F mutation may impact a potential weak binder in individuals who are DRB1*0101.

The coding mutations within the spike sequence are predicted to impact six "strong-binder" epitopes for people
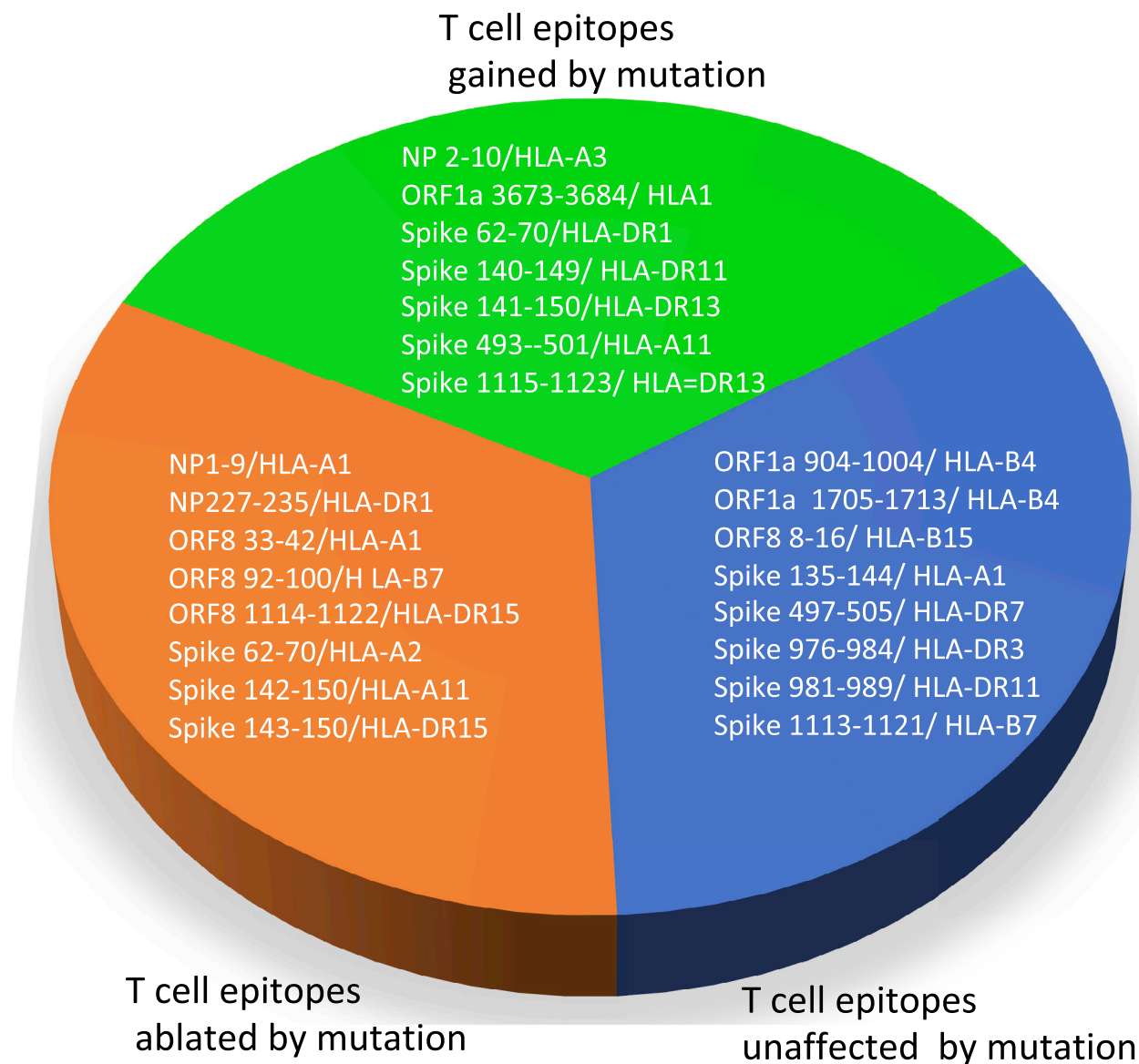
T cell epitopes gained by mutation

NP 2-10/HLA-A3
ORF1a 3673-3684/ HLA1
Spike 62-70/HLA-DR1
Spike 140-149/ HLA-DR11
Spike 141-150/HLA-DR13
Spike 493--501/HLA-A11
Spike 1115-1123/ HLA=DR13

T cell epitopes ablated by mutation

NP1-9/HLA-A1
NP227-235/HLA-DR1
ORF8 33-42/HLA-A1
ORF8 92-100/H LA-B7
ORF8 1114-1122/HLA-DR15
Spike 62-70/HLA-A2
Spike 142-150/HLA-A11
Spike 143-150/HLA-DR15

T cell epitopes unaffected by mutation

ORF1a 904-1004/ HLA-B4
ORF1a 1705-1713/ HLA-B4
ORF8 8-16/ HLA-B15
Spike 135-144/ HLA-A1
Spike 497-505/ HLA-DR7
Spike 976-984/ HLA-DR3
Spike 981-989/ HLA-DR11
Spike 1113-1121/ HLA-B7

Figure 1. Examples of predicted T cell epitope changes in recognition of B.1.1.7 relative to Wuhan sequence

carrying some HLA alleles. The 69–70 HV deletion is predicted to impair the binding of a strong binder in people who are DRB1*1501 while enhancing binding in those who are DRB1*0101; Tarke et al. found responses to this epitope restricted by DR15 or DR16.[13] The N501Y mutation would be predicted to generate a less stimulatory epitope only in people who are DRB1*0401. Similarly, the D1118 mutation would likely have differential effects depending on HLA type, with improved binding in people who are DRB1*0701 or DRB1*1501 but loss of the response in those who are DRB1*0301 or

DRB1*0401. Responses to this epitope have been found in a small minority of convalescent donors.[13] Looking at likely epitope changes resulting from mutations in the South African 501Y.V2 variant, note that most of the changes have little effect, and the key, E484K mutation does not overlap a predicted CD4 epitope. The 242-244 LAL deletion/R2461 mutation is predicted to impair the binding of a weak binder in people who are DRB1*0401 while enhancing binding in those who are DRB1*0101 and DRB1*0701. The D215G mutation is predicted to be associated with a loss of response in those who are

DRB1*0301 or DRB1*0401, and the mutation A701V is predicted to be associated with a loss of response in DRB1*0401.

To understand this in context, one needs to appreciate that, with fine-mapping of spike T cell epitopes very much still ongoing, around 280 CD4 epitopes have already been identified[13]; in individuals with a history of prior SARS-CoV-2 infection, on average, 3.2 and 2.7 proteins are strongly recognized by CD4$^+$ or CD8$^+$ SARS-CoV-2-specific T cells, respectively. None of the epitopes changed by the coding mutations seen in the B.1.1.7 and B.1.351 variants impacts the key

immunodominant or subdominant CD4 epitopes elucidated by Nelde et al.[14] As will be seen from the above analysis, such ablation of CD4 epitope recognition that does occur would impact differentially in people expressing different HLA alleles. Note also that mutations within a given epitope may yield one likely to be stronger as much as a weaker one: note, for example, that the 69–70 HV deletion in spike is predicted to generate improved immunogenicity for HLA-DR1 individuals but reduced immunogenicity for HLA-DR1501. T cell epitopes may be gained, lost, or unchanged in a variant compared to original sequence virus, as summarized in Figure 1.

While most attention on likely correlates of protection centers on neutralizing antibody titer and, to a lesser extent, on CD4 T cell response, it is likely that CD8 immunity is important, and this response is strongly correlated with the antiviral CD4 response. While some 450 CD8 epitopes have been described across HLAI alleles,[13] recognition of only 5 of these would be impaired (for some alleles) in an individual primed by natural infection or vaccination to the wild-type virus and then encountering the B.1.1.7 variant (Tables S1B and S1C). Note that, as seen for HLAII predictions, CD8 responses might be either gained or lost when challenged by variant sequence, depending on HLA type: the NP D3L mutation in B.1.1.7 causes gain of a predicted HLA*A301 epitope. The N501Y mutation leads to loss of a predicted strong binder in HLA*A101 individuals but gain of a predicted strong epitope in people who are HLA*A1101. For the South African 501Y.V2 variant, CD8 responses might be either gained or lost when challenged by variant sequence, depending on HLA type (Tables S1E and S1F).

From this analysis, it may be concluded that the B.1.1.7 variant has gained an advantage for population spread through several factors including enhanced ACE2 binding and greater potential for transmission due to increased copy number in the nasopharynx, but it is unlikely that it gains a substantial advantage through immune evasion at the level of either B cell or T cell recognition. There is a considerably higher degree of concern over the ability of mutations in the South African and Brazilian variants to evade immune memory elicited by wild-type spike vaccines, at least with respect to neutralizing antibody repertoire.

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