

CORONAVIRUS

SARS-CoV-2 T cell immunity: Specificity, function, durability, and role in protection

Daniel M. Altmann^{1*} and Rosemary J. Boyton^{2,3}

In efforts to synthesize a clear understanding of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) protective immunity, antibody analysis has been paralleled by T cell studies across asymptomatic, mild, and severe COVID-19 (coronavirus disease 2019). Defining CD4 and CD8 effector functions in protection is important, considering that antibody responses appear short-lived and T cell memory is potentially more durable. To fully understand population-level immunity, screening for both antibody and T cell immunity using standardized testing methods would be beneficial.

Analysis of T cell immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has progressed rapidly. Attention initially focused on characterizing antibody responses, dictated by translational need for diagnostic tests and seroprevalence data. With respect to vaccinology and therapeutics, impetus came from the likelihood that anti-spike neutralizing antibodies are a correlate of protection (CoP) (1). With time has come appreciation that among polymerase chain reaction–positive (PCR⁺) individuals are those that show both B cell and T cell immunity and those with a discordant response (2–4). The immune system is a complex network of interacting subsets, with adaptive immunity depending on cooperativity between T cell and B cell repertoires. We must concede that a confounder associated with SARS-CoV-2 is, seemingly, a degree of uncoupling between B cell and T cell priming and memory. A relatively ephemeral antibody response and a more enduring T cell immunity were predicted by experiences with the closely related Middle East respiratory syndrome (MERS) and SARS-CoV-1 infections (5, 6).

Here, we consider this and other key lessons from recent T cell immunology studies concerning lymphopenia and other perturbances of immune subsets, T cell exhaustion, cytokine programs, “cytokine storms,” target antigens, epitopes, and the contribution of viral cross-reactivity. From all that is known of viral immunology in general and coronavirus T cell immunity specifically, one might assume that SARS-CoV-2 T cell memory likely lasts for years and confers protection. This currently remains

hypothetical, awaiting formal proof of CD4 or CD8 immunity as a CoP, for example, through non-human primate protection studies (1).

From the earliest weeks of the pandemic, there have been unprecedented efforts to acquire immune datasets from hospitalized patient cohorts and then from exposed individuals in the community. One can already access published datasets, either as papers or as preprints, of observations from multiparameter flow cytometry and mass cytometry to whole proteome T cell epitope mapping, tetramer analysis, and single-cell RNA sequencing (3, 7–13).

Lymphopenia is a commonly observed correlate of severity (as judged clinically and by raised complement-reactive protein, D-dimer, and ferritin), especially within the CD8 subset (2, 12). In those who recover, this is reversible within a few weeks, with mild cases recovering faster. The findings have been interpreted as perhaps more likely to reflect sequestration of T cells to sites of infection rather than overt T cell ablation. A number of centers have sampled infiltrating cells both from lung tissue and from bronchoalveolar lavage (BAL); detailed characterization of these local immune subsets and their functions will be important. However, from data thus far, it is not clear that there is substantial displacement of T cells from the periphery to the lungs. Comparative analysis of BAL cells from moderate versus severe/critical disease indicates, if anything, that severe cases with the most overt lymphopenia have lower levels of CD8 cells in BAL, arguing against simple sequestration (13).

Across numerous studies, the basic observation in most infected people (except perhaps the most severe cases) is one of robust T cell activation and cycling, responding at a variably high frequency to many epitopes across many parts of the viral proteome. The effector response elicited is most simply categorized as “broadly T_H1 (T helper cell 1),” with CD4 responses somewhat dominant over CD8 and epitopes within spike antigen often at the top of a hierarchy of antigens throughout the proteome (Fig. 1). Details of this antigen hierarchy seem to differ somewhat with disease severity.

Responding T cells show a general activation phenotype, including expression of Ki67, CD38, and human leukocyte antigen–DR (HLA-DR) (3, 14). However, a number of studies also describe elevated coexpression of exhaustion markers, including programmed cell death protein 1 (PD-1) and T cell immunoglobulin mucin-3 (TIM-3). With transition from the initial observational studies to more reductionist investigations, it will be important to drill down to whether there are viral adaptations that indeed predispose, even during the acute response, to a profile more commonly associated with chronic activation, and whether this is associated with any impairment of passage into sustained, long-term memory.

Several laboratories have done detailed analyses of immune subsets and functional CD4 and CD8 responses across the disease spectrum from mild disease to intensive care unit (ICU) cases and death (Table 1). It is not yet known which T cell subsets are preferentially implicated in either protective or pathogenic immunity. CD4 and CD8 responses can be detected in most patients, with the CD4 response being seen more commonly (Table 1). If anything, responses are larger and broader (in terms of epitope coverage) in more severe patients (7). The fact that patients with very severe disease

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¹Department of Immunology and Inflammation, Imperial College, London W12 0NN, UK. ²Department of Infectious Disease, Imperial College, London W12 0NN, UK. ³Lung Division, Royal Brompton & Harefield NHS Foundation Trust, London, UK.

*Corresponding author. Email: d.altmann@ic.ac.uk

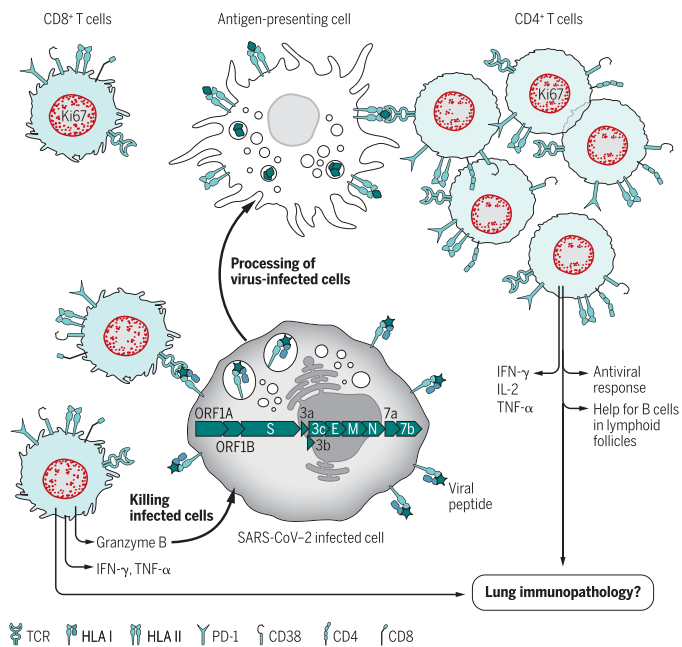


Fig. 1. Hypothetical interactions between SARS-CoV-2-infected cells, antigen-presenting cells, and CD4 and CD8 T cells. Viral peptides (shown in dark green) will be processed from all parts of the SARS-CoV-2 proteome and presented to the TCR repertoire in the grooves of HLA I molecules on the infected cell and by HLA II molecules of antigen-presenting cells that have taken up debris from infected cells. SARS-CoV-2-reactive CD4 cells appear to be largely T_H1 -like, secreting IFN- γ , TNF- α , and IL-2. CD8 cells can secrete a similar cytokine profile but also lyse infected target cells. We are unaware of data at present clearly indicating a role of CD4 or CD8 T cells in lung immunopathology, but illustrate here the hypothetical likelihood of this.

nevertheless show the strongest T cell signal is compatible with either a trivial explanation—more viral load for a longer duration primes more T cells—or a less trivial version: Large T cell responses may encompass a contribution to immunopathogenesis, such as lung damage.

Mapping SARS-CoV-2 epitopes targeted by CD4 and CD8 T cells, including any differences in recognition patterns between disease states from unaffected contacts to severe cases, has been a high priority in narrating the story of host defense. However, this is a nontrivial endeavor when dealing with small-volume, lymphopenic blood samples from severe patients and assaying a large and complex viral proteome that, depending on synthetic peptide length and overlap, requires a library of some 400 to 500 peptides. Differing approaches have sometimes yielded different answers with respect to antigen hierarchies. T cell assays have encompassed intracellular cytokine staining, assessment of T cell activation-induced markers, tetramer or pentamer frequencies, and ELISpots (enzyme-linked immunosorbent spots),

using either selected peptide pools or extremely large peptide megapools.

Findings with respect to antigen and epitope T cell recognition are summarized in Table 1. Considering the diversity of approaches and cohorts, a reasonable level of consensus is emerging. A number of studies find responses to spike epitopes to be the most abundant, followed by either the membrane antigen or nucleocapsid. Thus, both the B cell receptor and T cell receptor (TCR) repertoire seem rather focused on spike. However, as pointed out by Grifoni *et al.* (8), the antigen hierarchy within the SARS-CoV-2 proteome is more equally spread across the antigens than for the previously known coronaviruses, where more

than half of T cell recognition would be expected to target just spike epitopes. Generating datasets at speed with small blood samples and huge peptide pools, data on defining individual epitopes and peptide-major histocompatibility complex complexes have thus far come from only a few laboratories (7, 15). The data indicate a highly epitope-rich sequence, with some epitopes recognized commonly between individuals and between studies in different countries, such as the epitopes within nucleocapsid 81 to 120. The epitopes will need to be further defined and characterized in the context of presentation by specific human leukocyte antigen I (HLA I) and HLA II alleles. Those that are found to be commonly presented by several HLA alleles (sometimes called “promiscuous epitopes”) will be particularly useful for applications, such as comparative mapping of vaccine immunogenicity and design of diagnostic tests of T cell immunity. Furthermore, a precise understanding of preferential peptide presentation by HLA alleles will be needed to decode future datasets revealing

increased or decreased coronavirus disease 2019 (COVID-19) risk in populations with specific HLA polymorphisms.

A contentious area in SARS-CoV-2 immunity has been the extent to which there is cross-reactive immune memory from past infections by distantly related human coronaviruses (HCoVs). After the initial premise that the present outbreak has had such great impact, partly due to being a new introduction with no prior immunity in the population, antibody studies indeed indicated cross-reactivity, at least for some antigens; individuals never exposed to SARS-CoV-2 can demonstrate cross-reactive antibodies to the nucleocapsid (16). At the level of TCR recognition, it might be predicted that epitopes representing stretches of conserved sequence might confer cross-reactive recognition, even between viral sequences that have low overall sequence conservation. Studies have produced somewhat divergent answers, sometimes attributable to focusing on different antigens or using different measures of T cell recognition. A significant proportion of pre-COVID-19 blood donor samples show cross-reactive immunity to SARS-CoV-2 S and M peptide pools (4, 8). Studies have highlighted the presence of cross-reactive epitopes within the open reading frame 1 (ORF1) region that can elicit responses in non-SARS-CoV-2 immune people who presumably have been exposed to other HCoVs (15). Less surprisingly, people with immune memory for SARS-CoV-1 mount good, cross-reactive responses to SARS-CoV-2 (15). On balance, the evidence that a subset of people has a cross-reactive T cell repertoire through exposure to related coronaviruses is strong. The key point that remains to be determined is to what extent this could affect protection from disease. For example, is this a factor that could underpin decreased susceptibility in school-age children, presumed to be regularly boosted by exposure to common cold HCoVs?

A general observation from the patient cohorts is that most infected people make an antibody and a T cell response, the magnitude of the two often being correlated, and that, up to a point, more severe and protracted disease drives a larger response (17). However, it is also the case that in SARS-CoV-2 infection, measures of T cell and B cell recognition can become uncoupled, either because mild infection has triggered T cell immunity without detectable antibody or because the antibody response has been transient and already waned at a time

Table 1. Summary of published studies analyzing T cell responses to SARS-CoV-2. AIM, activation-induced marker; ARDS, acute respiratory distress syndrome; HC, healthy control; ICS, intracellular cytokine staining; nd, not done; M, membrane antigen; N, nucleocapsid antigen; S, spike antigen; T_{cm}, central memory T cells; PBMC, peripheral blood mononuclear cell; NSP, non-structural protein; CTLA-4, cytotoxic T lymphocyte-associated protein 4; RBD, receptor binding domain.

Manuscript	Methods	Cohort	T cell subsets and features	Antigen hierarchy	Epitope data	Cytokine/effector function	Cross-reactivity evidence
Braun <i>et al.</i> (14)	Spike peptide panel; AIM	Mild, severe, ICU COVID-19	CD38 ⁺ HLA-DR ⁺ activated T cells	Analysis limited to spike	nd	nd	Yes: A third of HC responded to C-terminal peptides from spike.
Thieme <i>et al.</i> (18)	Peptide panels; ICS	Moderate, severe, ICU COVID-19	<ul style="list-style-type: none"> • CD4 response detected in 95% • CD8 response in 77% 	M>S>N	nd	CD4 response: IFN- γ , IL-2, TNF- α ; higher frequency of polyfunctional cells in patients with greater severity	nd
Sekine <i>et al.</i> (3)	Peptide panels; ICS; AIM, tetramers	Moderate to severe COVID-19; exposed family members	<ul style="list-style-type: none"> • CD4: CD38⁺CD69⁺ Ki67⁺ PD-1⁺ • CD8: CD38⁺ CD39⁺ CD69⁺ CTLA-4⁺ HLA-DR⁺ Ki67⁺ LAG 3⁺ TIM-3⁺ "activated-cycling" phenotype 	M>N	Several predicted HLA-A and HLA-B predicted binders from the full proteome used to make tetramers	CD4 response: IFN- γ , IL-2, TNF- α ; T _H 1-skewed response CD8 response: IFN- γ , TNF- α , CD107a	Yes: cross-reactive recognition of spike and M
Peng <i>et al.</i> (7)	Peptide pools (not ORF1); ICS; ELISpot; pentamers; T cell lines	Recovered from mild to severe COVID-19	Higher magnitude and broader breadth of T cell responses in severe cases in comparison with mild cases	S>M>ORF3a	Spike: 18 peptides N: 10 peptides M: 6 peptides ORF3a: 4 peptides ORF7a: 3 peptides	IFN- γ , IL-2, and TNF- α polyfunctional response in both CD4 and CD8, mild, and severe cases	No: none observed in n=16
Grifoni <i>et al.</i> (8)	Mega-pools; AIM; ICS	Mild to severe COVID-19 and pre-2019 samples	Patients were convalescent and showed no evidence of lymphopenia.	S>M>N	Antigen mega-pools not resolved to the level of individual epitopes	CD4 response mainly IFN- γ ; CD8 is IFN- γ , TNF- α , and granzyme B	Half of HC showed cross-reactivity with RBD from HCoV OC43 or NL63.
Le Bert <i>et al.</i> (15)	Peptide pools from N, ORF3 NSP-7, and NSP-13	Mild to severe COVID-19 convalescent	Response in 100% to N epitopes	Study focus on N	N: 7 peptides	nd	All patients with SARS-CoV showed cross-reactive response to SARS-CoV-2 NP. Half of HC show cross-reactivity with epitopes in ORF-1 NSP-7 and NSP-13.

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Manuscript	Methods	Cohort	T cell subsets and features	Antigen hierarchy	Epitope data	Cytokine/effector function	Cross-reactivity evidence
Gallais <i>et al.</i> (4)	Peptide pools; ELISpot	Household contacts of 7 PCR ⁺ cases	Response in 100% of index cases and in seronegative contacts	S=M=N co-dominant	nd	nd	nd
Weiskopf <i>et al.</i> (12)	Mega-pools; AIM	ICU ARDS including fatal cases	<ul style="list-style-type: none"> • T cell lymphopenia • Most responder cells were T_{cm} based on CD45RA and CCR7 expression. 	S>"remainder of proteome mega-pool"	Antigen mega-pools not resolved to the level of individual epitopes	T cell culture supernatants contained: IFN- γ , TNF- α , IL-2, IL-5, IL-13, IL-10, IL-9, IL-17A, IL-17F, and IL-22	Cross-reactivity in 2 of 10 HC
Oja <i>et al.</i> (2)	Peptide pools; AIM; ICS; used PBMC and BAL	Mild, severe, ICU COVID-19	<ul style="list-style-type: none"> • T cell lymphopenia • PD-1 highest in most severe 	S>N>M>ORF3a. Spike response seen in BAL. Reduced response to spike and N in ICU cases	nd	Mainly IFN- γ and TNF- α . IFN- γ response significantly lower in ICU cases	No cross-reactivity found to spike peptides from S299E, S-OC43

when T cell memory is still robust. It is clear from these datasets that some people who lack an antibody response (and indeed may never have been formally defined as PCR⁺) show strong, specific T cell immunity (4, 18). This pattern is predicted by the experience with SARS-CoV-1 and MERS (5, 6). If, as appears the case, measuring T cell immunity is a more enduring and reliable marker of adaptive immunity in COVID-19 than antibody, it will be valuable to achieve rollout for health services of commercial T cell testing kits, as is done for tuberculosis diagnosis with QuantiFERON-TB Gold testing. The caveat is that although there is evidence for spike antibody as a CoP, we still await this evidence for T cells.

It can be seen in Table 1 that there is agreement that SARS-CoV-2-reactive T cells are overwhelmingly T_{H1}, sometimes with a poly-functional interferon- γ (IFN- γ), interleukin-2 (IL-2), and tumor necrosis factor- α (TNF- α) profile. This may be a beneficial profile, as severely unwell ICU patients showed reduced IFN- γ and a shift to a more T_{H2} profile (2). Many vaccine platforms are currently under investigation, each with different nuances of cytokine polarization. It is a given that the most protective vaccines may be the ones that can best achieve the protective cytokine profile (if only we were sure what this is) while avoiding stimulation of a T_{H2} response, which is predicted to be detrimental. Although there has been much attention to

cytokine storms as biomarkers of severity, from scrutiny of the cytokines involved, it seems more likely that this burst of cytokines originates predominantly from innate cells rather than from T cells.

In summary, progress since January 2020 has been impressive, but there is still so much more to learn. Are T cells protective and, if so, which are the key antigens and cytokine effector programs to focus on? Are all T cell responses beneficial, or are some contributory to immunopathology and to be avoided? If it is indeed the case that antibodies are transient and T cell memory is more durable (though, how durable?), what can we learn about anomalies of T follicular helper-B cell interactions in germinal centers? In the short-to-medium term, we need to ensure that all of this T cell toolkit and knowledge is brought to bear on robust, comparative evaluation of the different vaccine platforms, their immunogenicity, efficacy, and safety. Entering the next part of the battle, there are many thousands of people suffering from the chronic aftermath of infection posed by chronic, so-called "long-COVID" cases characterized by diverse symptoms, including fatigue, joint pain, and dyspnea (19). A more detailed understanding of the T cell immunology will be valuable in deciphering this pathogenesis.

At the start of the pandemic, a key mantra was that we needed the game changer of antibody data to understand who had been

infected and how many were protected. As we have learned more about this challenging infection, it is time to admit that we really need the T cell data too.

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Daniel M. Altmann and Rosemary J. Boyton

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