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T Cell Responses to SARS-CoV-2

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Abstract

A large body of evidence generated in the last two and a half years addresses the roles of T cells in SARS-CoV-2 infection and following vaccination. Infection or vaccination induces multi-epitope CD4 and CD8 T cell responses with polyfunctionality. Early T cell responses have been associated with mild COVID-19 outcomes. In concert with animal model data, these results suggest that while antibody responses are key to prevent infection, T cell responses may also play valuable roles in reducing disease severity and controlling infection. T cell memory after vaccination is sustained for at least six months. While neutralizing antibody responses are impacted by SARS-CoV-2 variants, most CD4 and CD8 T cell responses are preserved. This review highlights the extensive progress made, and the data and knowledge gaps that remain, in our understanding of T cell responses to SARS-CoV-2 and COVID-19 vaccines.

INTRODUCTION

This review is focused on T cell responses and SARS-CoV-2. A PubMed search using "(T cell OR T cells) AND (SARS-CoV-2 OR COVID)" in mid-June 2022 returned over 4,000 records. Accordingly, it is not feasible to fully review the literature, and we apologize for omission of papers not discussed here because of space limitations. Numerous quality reviews have discussed specific aspects of T cell responses and COVID-19 (1–13). This review is focused on recognized epitopes, duration of T cell responses, T cell responses in the context of infection-generated immunity and vaccination, cross-reactivity to other coronaviruses, and T cell recognition of variants. Virus-specific T cell responses can be detected following stimulation with defined or predicted epitopes, or in an unbiased fashion using overlapping peptide pools; much information is also generated by transcriptomic and systems biology approaches.

T CELL RESPONSES ARE DIRECTED AGAINST MULTIPLE ANTIGENS AFTER SARS-CoV-2 INFECTION

At the start of the pandemic, an immediate basic question to be addressed was whether significant T cell responses were induced by SARS-CoV-2 infection. Concerns were raised regarding potentially weak immunogenicity of coronaviruses. This would have implications for vaccine development, as T cell responses are important components of adaptive immunity (14). Conversely, while it was expected that cellular immunity would play a role in disease resolution, there was also considerable concern about the possibility that altered T cell responses could be in part responsible for COVID-19 acute respiratory distress syndrome (ARDS) (15, 16).

Early bioinformatic analyses highlighted that the main targets of adaptive immune responses to SARS-CoV-1 were relatively conserved in the new SARS-CoV-2 virus (17, 18), and they predicted that SARS-CoV-2 should be immunogenic for T cell responses. Grifoni et al. (19) showed that indeed SARS-CoV-2 was immunogenic, utilizing early convalescent SARS-CoV-2 infections causing mild disease to draw a portrait of the type of immune responses associated with uncomplicated COVID-19 disease resolution. CD4 and CD8 T cell, and IgG and IgA antibody, responses were all readily detected in the majority of individuals. Virus-specific CD4 T cell responses were predominantly Th1, generally with undetectable Th2 cells, easing concerns over Th2-type responses linked to immunopathology seen in certain animal models with other coronaviruses (20, 21).

The initial studies of Grifoni et al. also highlighted strong dominant CD4 and CD8 T cell responses to spike protein (sometimes denoted S) (19). This is in contrast to several other viruses where T cells predominantly recognize more prevalently nonstructural and internal virion proteins. This split dominance is observed in influenza virus (22–24) and flaviviruses (25, 26). This finding had remarkable positive implications, as it suggested that the vaccine development efforts underway based only on spike protein had the potential of inducing humoral, CD4 T cell and CD8 T cell responses. The reason for the dominance of spike as a target in SARS-CoV-2 infection is not fully understood, but both the large size of the protein (which thus encodes many epitopes) and its high level of expression (19) are likely to be contributing factors.

Other components of the SARS-CoV-2 proteome are also prominently recognized by T cells, including nucleocapsid (N), membrane (M), and nonstructural protein (NSP) antigens (19, 27–30). The recognition of these additional antigens suggested that these targets could be considered if a wide range of T cell responses became of greater interest in the context of vaccine design. The prominent recognition of certain NSP targets is particularly relevant in the case of cross-reactive T cells, as it lends to the potential development of pan-coronavirus vaccines (31).

In conclusion, SARS-CoV-2 infection elicits human adaptive responses involving humoral CD4 and CD8 T cell responses recognizing multiple antigens. The fine specificities and the functional features of T cell responses are discussed in the following sections.

EPITOPE SPECIFICITIES OF SARS-CoV-2 T CELLS

A large effort has been devoted to the characterization of the exact epitopes recognized by human T cell responses against SARS-CoV-2. As of June 2022, the published literature has expanded to more than 85 studies and identified over 2,000 unique CD4 and CD8 T cell epitopes, as cataloged by the Immune Epitope Database (10, 32, 33). These definition and characterization studies have enabled detailed analysis of the magnitude, kinetics, and phenotype associated with SARS-CoV-2-specific T cell epitope responses.

Only 20 of these studies analyzed a large spectrum of antigens, identifying epitopes from spike, N, M, envelope (E), and NSP. While there is good coverage of all antigens, 70 of the 89 studies probed spike, a bias perhaps justified by its immunodominance and use in vaccines. Approximately 15% (13 of 89) of the studies analyzed both CD4 T cell and CD8 T cell epitopes, while 29% analyzed only the former and 54% only the latter (**Supplemental Table 1**).

Supplemental Material >

Comparisons of the SARS-CoV-2-specific CD8 T cell epitope repertoires in vaccinees with those in infected individuals indicated broader spike-specific T cell responses in vaccinees. Additionally, booster vaccination of previously infected individuals increased spike-specific T cell breadth to levels similar to those in vaccinees, indicative of substantially overlapping epitopes (34).

Analysis of HLA restriction of SARS-CoV-2 T cell epitopes shows a bias largely reflecting allele frequency. For HLA class I, epitopes have been defined for 47 A, B, and C alleles, with a median of 14 epitopes per allele but a range of 1 to 246 (with the most for HLA-A*02:01). For HLA class II, epitopes have been defined for 51 alleles, with a median of 15 epitopes per allele but a range of 1 to 76 (with the most for DRB1*15:01). While HLA alleles can differ in epitope repertoire sizes (35), the alleles most frequently expressed are most often studied. **Figure 1*a*** illustrates the strong correlation between the frequency of HLA A and B alleles in the worldwide population and the number of associated SARS-CoV-2 CD8 T cell epitopes identified (Spearman correlation coefficient 0.79, $p < 0.001$). The frequency of HLA DRB1 alleles in the population and the number of CD4 T cell epitopes mapped are also well correlated (Spearman coefficient 0.80, $p < 0.001$)

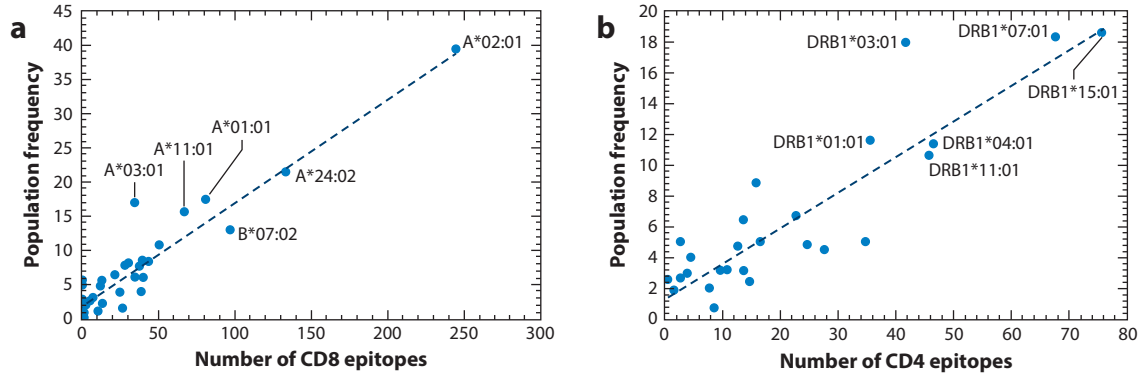

Figure 1

Relationship between frequency of individual HLA class I A and B, or HLA class II DRB1, alleles in the general worldwide population and the corresponding number of (*a*) CD8 T cell epitopes or (*b*) CD4 T cell epitopes identified. Coverage values were determined using the population coverage tool at **https://www.iedb.org/**, based on data obtained from the Allele Frequency Net Database.

(**Figure 1*b***). Contrary to what has been more typical of epitope identification studies in the past, there does not appear to be a bias toward identification of epitopes restricted by alleles prevalent in White people. In fact, the correlation in both cases is slightly lower when considering allele frequency in White populations (Spearman coefficients 0.75 and 0.76 for CD8 and CD4 T cells, respectively, $p < 0.005$). These results emphasize the value of including a diversity of ethnicities and populations (36) and reflect the truly worldwide nature of the scientific study of SARS-CoV-2.

No strong associations with specific class I or class II alleles have been reproducibly reported in genome-wide association studies of COVID-19 (37–40). In a minority of instances, children develop a serious syndrome called multisystem inflammatory syndrome in children (MIS-C), which has been reported to be associated with specific T cell receptors (TCRs) and with HLA-A*02, -B*35 and -C*04 alleles (41). Thus, while some alleles have been associated with different outcomes, many additional data are required to map potential links between different alleles and response or disease outcomes. However, the fact that thousands of SARS-CoV-2 T cell epitopes have been defined indicates a very large breadth of T cell responses against this virus. Thus, the epitope data suggest that at the population level it is unlikely that the virus would succeed in evading T cell responses by epitope mutation.

Some epitopes are immunodominant. Examples of these types of epitopes are the spike 269–277 (YLQPRTFLL) and the N 105–113 (SPRWYFYYL) CD8 T cell epitopes. For CD4 T cell responses, the M 176–190 (LSYYKLGASQRVAGD) and spike 166–180 (CTFEYVSQPFLMDLE) epitopes have been reported in multiple studies. Of considerable interest is to what extent the repertoire of epitopes recognized by T cell responses is limited to a narrow set of specificities. Some studies have reported very narrow repertoires, perhaps reflecting a relatively small number of subjects, peptides, or alleles. In several such cases (42–47), the repertoire was defined after an in vitro expansion and restimulation step, suggesting that the in vitro expansion might narrow the repertoire of specificities detected. Studies utilizing direct ex vivo assays tended to find larger repertoires (27, 48–54). In particular, Tarke et al. (51) reported a median of 10–11 CD4 epitopes and 10–11 CD8 epitopes recognized in spike-vaccinated individuals, with the epitopes recognized in different individuals being largely distinct, consistent with the heterogeneity of their HLA restriction elements.

In sum, a considerable amount of knowledge has accumulated on epitope targets of human T cell responses, which has highlighted the very large breadth of human CD4 and CD8 T cell responses to SARS-CoV-2. The epitope data suggest that most combinations of HLA alleles are capable of successful T cell responses against SARS-CoV-2.

T CELL ASSAYS AS A DIAGNOSTIC TOOL

The data above indicate that T cell responses should be considered a potential correlate of immunity, suggesting that T cell–based diagnostic assays for SARS-CoV-2 are feasible. Indeed, several studies have reported the feasibility of whole-blood IGRAs (IFN-γ release assays) (55–59) and demonstrated that SARS-CoV-2 IGRAs can detect T cell responses after infection or vaccination (60–63), including in immunocompromised subjects. Additionally, IGRA T cell tests are amenable to automation (64). SARS-CoV-2 ELISpot assays have also been developed for clinical use (65, 66), and CXCL10 mRNA measurements in whole-blood assays have been proposed to assess cellular immunity (67).

Choice of antigen and assay format is critical to discern different clinical, subclinical, and cross-reactive preexisting immunities (68). One approach is a spike IGRA for detecting COVID-19 vaccine responses and an N IGRA for SARS-CoV-2 infection responses (69). Differential reactivity to peptides derived from spike versus the remainder of the proteome can be used to distinguish preexisting reactivity, infection, and vaccination status (70). This classification was

effective with different vaccines and after different lengths of time after infection or vaccination and was associated with greater accuracy than serological classification.

In conclusion, multiple methodologies have been developed to measure T cell responses for potential diagnostic application. However, much work still needs to be done to develop assays that are easy to use, are well standardized, and provide rich granularity about the T cell responses.

ANIMAL MODELS INDICATE A ROLE FOR T CELL RESPONSES IN PREVENTION OF SYMPTOMATIC DISEASE

The importance of studying SARS-CoV-2-specific T cells in humans is supported by several lines of evidence generated in animal model systems. While a comprehensive review of these data is beyond scope here, several key lines of evidence need to be highlighted. A study investigating SARS-CoV-1 and Middle East respiratory syndrome (MERS) T cell responses showed that airway CD4 T cells mediate protective immunity against emerging respiratory coronaviruses in mice (71) and the protection was mediated by IFN-γ. Virus-specific memory CD8 T cells also provided substantial protection from lethal SARS-CoV-1 infection of mice (72). A major challenge of SARS-CoV-2 mouse models is that fatal outcomes occur exceptionally quickly, minimizing the amount of time T cells could conceivably contribute to protection. In murine models of SARS-CoV-2 infection, Zhuang et al. (73) showed that in the absence of neutralizing antibodies, systemic or lung-resident memory CD4 and CD8 T cells could provide effective protection. Vaccination with a single CD8 T cell epitope can protect mice against SARS-CoV-2 infection in the absence of neutralizing antibodies, via tissue-resident memory T cells (74).

In nonhuman primate SARS-CoV-2 models, several studies have found roles for CD8 and CD4 T cells in protective immunity, discussed in greater detail elsewhere (12). McMahan and colleagues directly showed that depletion of CD8 T cells in convalescent animals reduced protection against SARS-CoV-2 rechallenge (75). These results were extended in subsequent studies addressing vaccine-mediated protection against Omicron, showing correlations between CD8 T cell frequencies and lower viral loads after challenge (76). A different study did not observe a role of T cells, but the cell depletions in lymphoid tissue were unfortunately only partial, rendering that experiment uninterpretable (77). A role for CD8 T cells in vaccine-induced protection in macaques was also reported using an intranasal vaccine expressing viral non-spike antigens (78). In conclusion, several lines of evidence in diverse animal models show the value of T cell responses in protection from COVID-19.

T CELLS AND DISEASE SEVERITY IN UNVACCINATED INDIVIDUALS

Highly divergent COVID-19 disease outcomes are observed in unvaccinated individuals. Studies have characterized relationships between SARS-CoV-2-specific adaptive immune responses and COVID-19 outcomes. Early SARS-CoV-2-specific CD4 T cell responses were found to have the strongest association with reduced disease severity (compared to CD8 T cell and antibody responses) (79–81), and poor CD8 T cell responses were also associated with poor prognosis (79, 82). Early antibody responses did not correlate with better disease outcomes. Early T cell responses were associated with more rapid viral clearance and less severe disease in COVID-19 patients (83). Rapid type I interferon responses and virus-specific CD8 T cell responses were associated with nonsevere SARS-CoV-2 infections, while antibody development lagged by one to two weeks (84). Mild COVID-19 was also associated with high T cell polyfunctionality and high IL-2 and inversely correlated with anti-spike IgG levels (85).

Heterogeneity in CD8 T cell functionality is also related to disease outcomes. Increases in activation/exhaustion markers are seen in mild disease, compared to severe disease, while

sustained dysregulation linked to activation/exhaustion markers has been observed in hospitalized patients (86–89). Studies using MHC-I tetramers reported that the SARS-CoV-2-specific PD-1-expressing CD8 T cells in blood are not exhausted, suggesting that this subset might be associated with functional immunity (90). Delayed CD8 T cell responses may be associated with severe COVID-19 due to a failure of T cells to control viral replication in the lungs sufficiently fast (5).

SARS-CoV-2 infection, in the majority of cases, leads to adaptive antigen-specific responses, viral clearance, and creation of immune memory. COVID-19 can also be associated with powerful dysregulatory effects (91, 92). Immune dysregulation is a common element associated with SARS-CoV-1, MERS, and SARS-CoV-2 infection disease pathogenesis, typically associated with delayed innate interferon responses, delayed adaptive immunity, and exuberant inflammatory responses (5, 93, 94). Of relevance to the still poorly understood long COVID-19 syndrome (95), several studies highlight how some of these alterations last into the convalescent phase (85, 96–98). SARS-CoV-2-specific CD4 T cells responding to infection are predominantly of the Th1 and T follicular helper (Tfh) types (79, 99), and ARDS was not associated with excessive or altered virus-specific CD4 T cell responses (79). Evidence of increases in total activated CD8 T cells was observed in some individuals with severe COVID-19, possibly indicative of bystander CD8 T cell activation (89). An imbalance of regulatory and cytotoxic SARS-CoV-2-reactive CD4 T cells in blood was associated with greater COVID-19 disease severity (100). T cell IFN-γ in absence of perforin was associated with severe disease (85). A longitudinal study correlated early CD4 and CD8 T cell activation with mild disease (88).

Most studies directly examining T cells in lungs of COVID-19 patients found fewer CD8 T cells in patients with severe or fatal disease, indicating that severe COVID-19 is most associated with a lack of a successful T cell response (80, 101–105). In contrast, high levels of innate cells such as neutrophils and monocytes are present in the lungs of individuals with fatal COVID-19 (106–109). Aberrant late type I interferon responses are associated with prominent lung tissue destruction (104, 105, 110).

T cell responses occur in asymptomatic SARS-CoV-2 infection, providing another positive association between T cell responses and lack of symptomatic disease (111–113). Additionally, it has been noted that SARS-CoV-2-specific T cells are detectable in seronegative exposed family members (114) and that SARS-CoV-2-specific T cells were more often detected in intrafamilial exposures (not confirmed cases) compared to unexposed subjects (115, 116). Other studies have implied that cross-reactive CD4 T cell responses might be able to confer disease protection and be associated with abortive infection (117, 118).

Tfh cells are important for neutralizing antibody responses, and higher frequencies of circulating Tfh (cTfh) cells have been associated with milder COVID-19 (119). In a longitudinal study of convalescent subjects (120), mild disease was associated with a greater percentage of cTfh and Th1 cells among SARS-CoV-2-specific cells, which in turn correlated with sustained anti-spike antibody responses following viral clearance. Furthermore, SARS-CoV-2 CD4 T cell responses predict subsequent magnitude, breadth, and duration of neutralizing antibody responses (121). Conversely, the magnitude and quality of T cell responses correlated with neutralizing antibody titers after infection (122).

Systems biology approaches have provided a complex picture of changes associated with severe COVID-19 and death (123, 124), and comparisons of mild versus severe disease (92, 119, 125). Single-cell multi-omics analyses have highlighted lack of coordination between innate and adaptive responses in progressive COVID-19 (126) and alterations in ratios of different cell subsets as a function of disease severity (119). Genome-wide association studies have provided some potential biomarkers of COVID-19 severity and mortality (37, 127–130). Transcriptome-wide

association studies combined with cell type-specific expression quantitative trait loci (eQTLs) have implicated CXCR6, CCR9, and ARL17A in T cells as COVID-19 risk factors (129). The repeated implication of type I interferon pathways as central players in SARS-CoV-2 immune evasion and pathogenesis (94) most likely has important implications for T cell responses to SARS-CoV-2, as type I interferons are important regulators of T cell priming and effector cell differentiation (5).

INFLUENCE OF AGE AND SEX ON T CELL RESPONSES

It is well recognized that age and innate immunity are major variables affecting the clinical outcome of SARS-CoV-2 infection, with sex and comorbidities also affecting COVID-19 outcomes. T cell responses to SARS-CoV-2 infection are influenced by age, with lower T cell responses being associated with smaller pools of naive T cells available in elderly people to mount responses to new antigens (79). This may also be exacerbated by changes in innate immunity with age (131). The influence of age on disease outcomes and T cell immunity as it relates to children is of particular relevance, as recently reviewed (132, 133). At the level of SARS-CoV-2-specific T cell responses, there are conflicting reports regarding the relative strength of responses in children compared to adults (134, 135). Regarding sex as a biological variable, in two large studies, no differences were observed in SARS-CoV-2-specific memory CD4 T cell or CD8 T cell frequencies between females and males after infection (29, 30).

Taken together the data discussed in the sections above exemplify positive associations between robust SARS-CoV-2-specific early T cell responses and less severe COVID-19 in unvaccinated individuals. Besides differences in magnitude of responses, phenotypic features and T cell subsets are associated with disease severity. These data must be interpreted with caution, both because of their correlative nature and because CD4 T cells (Tfh cells) are also central to the development of potent neutralizing antibody responses.

FUNCTIONALITY OF T CELL RESPONSES AND ANATOMICAL LOCATION IN SARS-CoV-2 INFECTION

An issue of considerable importance in understanding infection is the relationship between systemic and tissue-localized immune responses in mucosal and respiratory tissues (136) and germinal centers (GCs) and other lymphoid sites. The topic of innate and adaptive immune responses in the lung and airways in the two cases of influenza virus and SARS-CoV-2 was recently reviewed (137). Local tissue T cells are likely relevant for COVID-19-protective immunity (12). Both CD4 and CD8 T cell responses are readily detected following SARS-CoV-2 infection in the upper respiratory tract (138, 139). This parallels findings of earlier studies (140) showing that vaccine-generated tissue-resident memory T cells in the lung provide heterosubtypic protection from influenza virus infection. Likewise, T cell responses are detected in the lung following SARS-CoV-2 infection, even in some individuals for whom SARS-CoV-2-specific T cells in the periphery are not detectable (141–143).

An early study reported that cTfh cell responses were readily detected in recovered COVID-19 patients (144). Numerous subsequent studies have demonstrated SARS-CoV-2-specific Tfh cell responses after SARS-CoV-2 infection, with some associations between cTfh cell frequencies and neutralizing antibody titers (30, 120, 145, 146). Notably, severe or fatal COVID-19 can be characterized by profound disruption of GCs and loss of Bcl-6-expressing GC-Tfh cells (147, 148).

Analyses of SARS-CoV-2 seropositive organ donors revealed that CD4 and CD8 T cells and memory B cells generated in response to infection are present in the lung, bone marrow, spleen, and multiple lymph nodes for at least six months after infection (142). Importantly, these studies demonstrated significant correlations between circulating and tissue-resident memory T and

B cells, thus supporting the validity of measures taken in blood as convenient, albeit imperfect, proxies for tissue-localized immunity.

In conclusion, variations in T cell subpopulations that are a function of anatomical location are an important factor to consider, and they likely differ substantially when between infection and systemic vaccination. These observations support the interest in alternative and mucosal vaccine delivery. At the same time, the current data suggest that, albeit imperfect, analysis based on the study of peripheral T cells is a valid approach to define overall T cell responses.

DURABILITY OF T CELL RESPONSES FOLLOWING INFECTION

It is of obvious relevance, for management of the pandemic, to study which attributes of immune memory are associated with long-lasting immunity after infection. Quantifying the durability of T cell responses elicited by infection is a component of these assessments. T cell immune memory after SARS-CoV-2 infection was recently extensively reviewed (11). In brief, memory CD4 and CD8 T cell responses are observed in the majority of infected individuals for over eight months with only modest declines in cell frequencies over that period (29, 30, 149–152), indicating that circulating CD4 and CD8 T cell memory is likely to persist for many years after SARS-CoV-2 infection (30). Responses were shown to be durable regardless of disease severity, as durable memory T cells were also reported to be present following asymptomatic infection (153). Durable T cell responses following SARS-CoV-2 infection are also supported by reports of T cell memory of SARS-CoV-1 up to 18 years after infection (154, 155). Of note, while memory CD4 T cells are detectable in the vast majority of SARS-CoV-2 infections, ~30% of individuals did not have detectable circulating functional memory CD8 T cells, suggesting that there may be impairment of memory CD8 T cells in a fraction of individuals (30).

T CELL RESPONSES INDUCED BY SARS-CoV-2 VACCINES

Vaccines have undoubtedly been the most effective tool to combat COVID-19 and SARS-CoV-2 infections. Their development in record time will likely go down in history as one of the most prominent accomplishments of medicine in the twenty-first century (156). A variety of vaccine platforms have been tested in humans, and several have been approved for human use (157, 158), with ChAdOx1 nCoV-19 (AZD1222), CoronaVac, Pfizer BNT162b2, Sinopharm, and Moderna mRNA-1273 being the most widely used (156). These represent adenoviral vector, inactivated virus, and mRNA technologies.

For adenoviral vector vaccines, early analysis of T cell responses induced by the ChAdOx1 nCoV-19 vaccine found polyfunctional Th1 CD4 T cells and CD8 T cells following a single dose (159, 160) or a prime boost regimen (161), and these were detected after several months (162, 163). CD4 and CD8 T cell responses to the Janssen/J&J Ad26.COV2.S vaccine were detected by spot-forming, activation-induced marker (AIM), and intracellular cytokine staining (ICS) assays (164–166) and were durable for at least six to eight months (166, 167).

For inactivated virus vaccines, CD4 T cell responses occur, but CD8 T cell responses are generally not generated, as expected (168–170). The inactivated virus vaccine platform does have one potential advantage of inducing responses to N, in addition to spike. Non-spike antigens are more conserved than spike and are thereby of interest in the context of variant recognition (169, 170).

In the case of mRNA vaccines, CD4 and CD8 T cell responses were initially detected following BNT162b2 vaccination (171) and were maintained over several months (172). For Moderna mRNA-1273, T cell responses were also detected, though initially minimal CD8 T cell responses were reported, presumably because of the specific details of the assay used (173). CD4 and CD8 T cell responses to BNT162b2 or mRNA-1273 were durable up to seven months after initial

immunization, as detected by the use of AIM and overnight ICS protocols (166, 174). Wherry and colleagues reported longitudinal T cell responses following mRNA vaccination of uninfected or COVID-19-recovered individuals (146, 175). One study reported higher CD8 T cell responses in females in the context of responses to mRNA vaccination (176). Finally, protection following a single dose of mRNA vaccine was associated with the appearance of T cell responses (177–179).

Circulating Tfh cells have been found following mRNA vaccination (146, 175). Fine-needle aspiration of lymph nodes has allowed investigators to directly study GCs following vaccination in humans (180, 181). These studies have clearly demonstrated the role of Tfh cells in generating antibody responses to the COVID-19 RNA vaccines. Furthermore, Tfh cell and GC deficiency has been demonstrated in the defects in COVID-19 mRNA vaccine responses by immunocompromised kidney transplant recipients (180). Notably, GC responses in lymph nodes correlated strongly with the development of neutralizing antibodies (181). Using a particular DRB1*15:01/S751 tetramer, one study was able to track CD4 T cells and cTfh cells and provided a detailed account of evolution of these responses to infection and mRNA vaccination, including boosters (145).

Additional vaccine platforms have been reported to induce T cell responses in humans. The recombinant spike protein plus adjuvant vaccine NVX-CoV2373 developed by Novavax provided high levels of protection in efficacy trials and is used in several countries (182). This vaccine has been reported to induce vigorous CD4 T cell responses (183), including cTfh and Th1 cells (166, 184). CD8 T cell responses to NVX-CoV2373 were sporadically detected, which is uncommon for recombinant protein vaccines and may be related to the adjuvant used (166, 184). The adjuvanted whole inactivated virion vaccine BBV152/Covaxin elicits CD4 T cell responses, including substantial frequencies of cTfh cells (170). Among many alternative COVID-19 vaccines being explored, one includes the spike and N antigens delivered by a modified vaccinia virus Ankara vector; T cell responses to both spike and N were detected (185). One T cell epitope peptide vaccine, CoVac-1, consists of conserved class I and class II epitopes from spike, N, M, E, and ORF8 suspended in an oil-in-water adjuvant containing a TLR1/2 (Toll-like receptor 1/2) ligand. CoVac-1 has been tested in a phase 1 trial and successfully elicited both CD4 T cell and CD8 T cell responses in 80–100% of individuals (186). An intranasal T cell peptide vaccine in a monkey model of COVID-19 resulted in 100-fold-lower peak viral loads (78).

In conclusion, several of the SARS-CoV-2 vaccines that have been tested in humans have been analyzed for induction of T cell responses. Direct comparisons of T cell responses between vaccines are reviewed below.

COMPARATIVE STUDIES OF T CELL INDUCTION BY DIFFERENT VACCINE PLATFORMS

For accurate quantitative and qualitative assessments of T cell responses elicited by different vaccines, head-to-head comparisons are needed. Several studies have compared antibody responses to different vaccines, which is substantially easier due to the nature of serum sample storage. In healthy adults, mRNA-1273 induced the strongest neutralizing antibody responses, which were slightly stronger than those induced by BNT162b2, and responses to both of these vaccines were greater than those induced by either of the adenoviral vector vaccines AZD1222 and Ad26.COV2.S (166, 187–189). In the largest comparison of the two mRNA vaccines mRNA-1273 and BNT162b2 (over 1,000 individuals), peak antibody binding titers were 2.6-fold higher to mRNA-1273 (190). Dashdorj et al. (191) compared antibody responses to four SARS-CoV-2 vaccines in Mongolia, with lower responses observed in the case of Sinopharm and Sputnik V vaccines in comparison to the AstraZeneca or Pfizer/BioNTech vaccines. In comparison to infection, mRNA vaccine–elicited antibody titers waned much faster (192).

Recent studies compared CD4 T cell, CD8 T cell, antibody, and memory B cell responses to four COVID-19 vaccines in humans: BNT162b2, mRNA-1273, Ad26.COV2.S, and NVX-CoV2373, representing three different vaccine technologies (51, 166). The mRNA and the protein plus adjuvant vaccine platforms were found to be most immunogenic in terms of CD4 T cell responses (51, 166). All of the vaccines generated detectable CD4 T cell responses in close to 100% of individuals; Th1 and cTfh cell responses dominated. GzmB-expressing cells with CD4-CTL (cytotoxic T lymphocyte) characteristics were also detected after mRNA or NVX-CoV2373 vaccination (166). Peak neutralizing antibody titers generally tracked with the magnitude of the CD4 T cell responses against spike. In the case of CD8 T cell responses, the mRNA platforms were associated with stronger responses as compared to Ad26.COV2.S (51, 166). Overall, CD4 T cell, CD8 T cell, and cTfh cell responses to each of these vaccines were equivalent or superior to those observed against spike in the context of SARS-CoV-2 infection (166, 193). Several other studies report similar findings (174, 175, 187), although researchers using shorter CD8 T cell stimulation (6–8 h instead of overnight) tended to observe weaker overall CD8 T cell responses, with responses preferentially detected in Ad26.COV2.S-immunized individuals compared to mRNA-immunized individuals (194–196).

T cell responses have also been compared head-to-head for several other vaccines. ChAdOx1-primed immune subjects given a booster with BNT162b2 induced significantly higher frequencies of spike-specific CD4 and CD8 T cells than individuals receiving two ChAdOx1 doses (163, 197). Similar results were obtained for mRNA boosters after immunization with the adenoviral vector vaccine, Ad26.COV2.S (195, 198). Peng et al. (199) compared BNT162b2 and CoronaVac vaccinations in approximately 60 subjects in Hong Kong; antibodies and CD4 T cells were detected, with weaker spike-specific CD4 T cell responses induced by CoronaVac. No CD4 T cell responses were noted against the N antigen in the CoronaVac group (199). The Sinopharm BBIBP inactivated vaccine induced a weaker CD4 T cell response in comparison to mRNA vaccines, but it did result in detectable responses to both spike and N in another study (200). In a study examining T cell responses to both Sinopharm and CoronaVac inactivated vaccines, researchers observed no difference in T cell responses between the two vaccines and found substantially stronger T cell responses in mRNA-vaccinated individuals (201). These results, in terms of relative capacity to induce humoral and T cell responses in general, correlate well with vaccine efficacy comparisons reported by various studies (156, 187, 202).

In conclusion, the available head-to-head comparisons of different vaccine platforms indicate that the mRNA platform induces the strongest CD4 and CD8 T cell responses compared to viral vector platforms. Protein adjuvanted and inactivated vaccines also induce appreciable CD4 T cell responses but are substantially less effective in inducing CD8 T cell responses.

DURABILITY OF VACCINE-INDUCED T CELL RESPONSES

Immune memory to COVID-19 vaccines has recently been reviewed elsewhere (11). The brisk antibody responses induced by two-dose mRNA vaccination wane significantly, by a factor of 8 to 10 over the course of six months (174, 192). In contrast, CD4 T cell memory and CD8 T cell memory waned by a factor of 2 or less (166, 174). Similar findings have been reported using MHC-I tetramers (145) and for studies using a variety of other T cell assays, with somewhat reduced T cell cytokine detection at six months (203, 204). While strong boosting of humoral responses was observed in hybrid immunity conditions, more limited boosting of T cell responses was noted (205).

In terms of long-term vaccine efficacy, the interpretation of the data and comparisons of vaccines and previous infection are complicated by the impact of variants and boosters. Even with relatively low neutralizing antibody titers, previous infection provided substantial protection

against symptomatic disease through at least the Delta variant of concern and substantial protection against severe disease with Omicron (11, 206). Individuals who received two doses of an mRNA vaccine predominantly had undetectable levels of neutralizing antibodies against Omicron and still had substantial immunity from severe disease (207–209). Neutralizing antibodies are a clear correlate of protection for prevention of SARS-CoV-2 infection in mRNA-vaccinated individuals (210). In vaccinated individuals, neutralizing antibody responses are highly likely to be most crucial in protection from infection, while cellular immunity likely plays important roles in protecting from severe disease and hospitalization. Potential roles of memory CD4 T cells, memory CD8 T cells, and tissue-resident T cells in protective immunity against COVID-19 are extensively reviewed elsewhere (11, 12).

T CELL RESPONSES IN IMMUNOCOMPROMISED PEOPLE, CANCER PATIENTS, AND OTHER VULNERABLE GROUPS

Immunocompromised individuals represent an important category of vulnerable subjects, and it is important to determine whether they generate humoral and T cell responses following vaccination. For example, humoral responses would be expected to be less impacted in patients with immune-mediated inflammatory diseases, and individuals with HIV infection and normal CD4 T cell counts, as compared with hematological cancer patients and patients treated with B cell–depleting agents (e.g., anti-CD20 therapy) (211).

Several studies reported good vaccine-induced SARS-CoV-2-specific T cell responses in inflammatory disease patients undergoing immune-modifying therapies (212–214), suggesting that some degree of T cell–mediated protection from severe disease might be available in these patients. Encouragingly, reactivity was preserved also against Delta (213) and Omicron (212) variants of concern. High T cell response rates and similar magnitude of responses after one to three COVID-19 vaccinations have been reported in recipients of B cell–targeted therapies such as anti-CD20 or anti-BAFF (215–219), despite severely reduced humoral responses.

Vaccine responses in patients with cancer or a range of inflammatory diseases may be confounded by the multiple treatments the patients receive and altered immune status from the disease itself. Multiple sclerosis patients who received anti-CD20 treatment and have depleted levels of B cells are of particular interest because of their relatively otherwise intact immune system. These patients made robust CD4 and CD8 T cell responses to mRNA vaccines (220–222) that were boosted by successive immunization (223). Similar findings were noted for rheumatoid arthritis patients treated with B cell depletion therapy (224). However, for both of these cohorts (multiple sclerosis and rheumatoid arthritis) it is still not established to what extent these T cell responses are associated with protection from severe disease (225).

Organ transplant recipients are immunosuppressed. The degree of immunosuppression depends on the type of transplant and the time since transplantation. Kidney transplant recipients have surprisingly poor responses to COVID-19 vaccines, though a third dose of mRNA vaccine has been successful in many (226), with spike-specific CD4 T cells being the best predictor of responsiveness among patients who did not make substantial (receptor binding domain) IgG after two doses of mRNA vaccine (227). Lymph node fine-needle aspirations in vaccinated kidney transplant recipients have revealed that these individuals usually have poor GC Tfh cell responses, which may underlie their poor GC and neutralizing antibody responses to COVID-19 vaccines (181).

Cancer patients have higher risk of severe COVID-19 (228). For individuals with solid tumors, both cellular and antibody responses to mRNA vaccination are usually not impaired (229). Hematologic malignancies are a special case (230). In patients with lymphoma undergoing

anti-CD20-mAb therapy, humoral responses were drastically reduced, whereas T cell responses were observed in the majority of these subjects and were similar in frequency to those observed in controls (231). However, the CD4 T cell responses appeared to be delayed, suggesting that the absence of B cells may impair the CD4 T cell response. In lymphoma patients not on B cell–depleting therapy, low CD8 T cell counts or low CD4 T cell counts were the highest risk factors for COVID-19 mortality (232). CD8 T cells contribute to survival in patients with COVID-19 and hematologic cancer even in absence of B cells (233). Among hospitalized cancer patients who recovered from COVID-19, both chemotherapy and B cell depletion were associated with increased risk of persistent infection, which appeared to be more likely in patients with low CD4 T cell counts (232). Notably, strong CD4 T cell responses were associated with viral clearance in B cell–depleted subjects with hematological cancers (234). Overall, this combination of findings is consistent with a model in which antibodies, CD4 T cells, and CD8 T cells work together in controlling COVID-19 and missing any one of the three is a risk factor for worse outcomes.

In conclusion, immunocompromised subjects respond to COVID-19 vaccination to different degrees. Alterations in the B cell compartment correspond to decreased humoral responses to COVID-19 vaccines, but in general CD4 T cell and CD8 T cell responses are conserved. Indeed, several studies show that vaccination and boosters of immunocompromised individuals are associated with significant protection (235–237).

HOMOLOGOUS AND HETEROLOGOUS IMMUNIZATION EFFECTS ON T CELL RESPONSES

As the pandemic progressed, waning of vaccine-induced protection against infection became apparent. Booster vaccinations have been widely utilized to counter waning immunity. Heterologous prime boost immunization strategies have been investigated for over 20 years as a means to enhance immune responses in the context of many indications such as malaria and HIV. The availability of a diversity of SARS-CoV-2 vaccination platforms allowed the potential benefits of heterologous prime boost vaccination to be addressed in humans.

In the case of booster vaccinations with mRNA-1273, Ad26.COV2.S, or BNT162b2, the strongest increases in both antibody and CD8 T cell responses were observed for mRNA booster vaccination of subjects originally vaccinated with Ad26.COV2.S; mRNA-1273 was associated with the strongest CD4 T cell responses in both homologous and heterologous regimens (195). Similar findings were obtained in a separate study where BNT162b2-BNT162b2 immunization outperformed Ad26.COV2.S-BNT162b2 immunization (238).

Several studies reported positive effects of a third (239–241) booster dose with the CoronaVac inactivated vaccine on T cell responses, and increased T cell responses in individuals immunized with inactivated vaccines who received mRNA boosters (201, 242). Heterologous booster with Sinovac induced a lower T cell response in comparison to mRNA vaccines (200). mRNA vaccines were able to boost T cell and antibody responses in individuals previously vaccinated with Sinovac or CoronaVac (201).

Pozzetto et al. (243) reported better protection against infection by heterologous ChAdOx1–BNT162b2 vaccination compared with homologous BNT162b2, though differences in dose interval and age groups may have contributed to the different outcomes. A Swedish study (244) found that COVID-19 vaccination using ChAdOx1 nCoV-19 prime followed by homologous ChAdOx1 booster or BNT162b2 or mRNA-1273 heterologous boosters was 50%, 67%, or 79% effective, respectively, against symptomatic infection. Similar results were reported in a Brazilian study (245). A study of vaccine efficacy against symptomatic infection showed lowest efficacy for one or two doses of ChAdOx1, greater efficacy for mRNA boost of ChAdOx1, and best for three doses of mRNA (246).

In some mix-and-match vaccination studies, effects may be confounded by changes in the interval between the vaccinations. The impact of varying time intervals between first and second immunization on vaccine responses in general, and on T cell responses in particular, is of interest with regard to basic immunology, policy setting, and pandemic management. Extending the intervals between immunizations with BNT162b2 mRNA vaccine to 6–14 weeks, compared with 3–4 weeks, resulted in higher antibody responses and a modest shift toward IL-2$^+$ CD4 T cells (172). Hall et al. (247) also observed enhanced antibody titers, but no change in T cell responses, suggesting changes in interval have only a modest impact on T cell memory.

Seven COVID-19 vaccines were tested as third-dose boosters following a primary immunization series (two doses) of ChAdOx1 nCoV-19 or BNT162b2 (248): BNT162b2, ChAdOx1, mRNA-1273, NVX-CoV2373, protein vaccine VLA2001, Ad26.COV2.S, and CureVac CVnCov. An irrelevant vaccine was used as a control. Individuals receiving mRNA boosters generally had the highest peak antibody titers, though many vaccine boosters were in a similar range, and durability of the antibody titers was not reported (248). mRNA-1273 provided the largest boost in T cell responses, both in subjects <70 y old and in those >70 y old, while NVX-CoV2373 and BNT162b2 also provided significant boosts in both T cells and antibodies.

In conclusion, while heterologous immunization with an mRNA vaccine has clear evidence of improved immune responses in most studies, no consistent gain was observed with heterologous boosters with adenoviral vectors or inactivated virion vaccines. Third-dose booster immunizations can improve T cell responses as well as antibody responses, depending on the vaccine combination. Substantially more research is warranted to understand the detailed characteristics of T cell responses under these different conditions, and their durability.

HYBRID IMMUNITY AND BREAKTHROUGH INFECTIONS

Vaccination of previously infected subjects is associated with development of a distinct immune response, often called hybrid immunity (206, 249, 250), that is superior to what is observed after only vaccination or previous infection. This observation provided strong support for the notion that people that recovered from infection still benefit from vaccination. This was confirmed by studies that showed vaccine efficacy and durability were enhanced in previously infected subjects who got vaccinated (251, 252). The effect is most striking at the level of antibody responses, but also has been detected in T cell responses (70, 250). Other studies reported that the effect on T cell memory was not apparent at three months (175) or that hybrid immunity was associated with increased antibody responses but a similar magnitude of T cell responses (253). Nantel et al. (254) describe hybrid immunity at the level of both cellular and serological responses after BNT162b2 vaccination, and the effects were most prominent in subjects with prior symptomatic infection. Previously infected subjects given one BNT162b2 dose achieved T cell response levels comparable to those of uninfected subjects who received two vaccine doses (205). Beyond spike-specific responses, hybrid immunity results in recognition of a much broader set of epitopes, including many non-spike antigens, which is also reflected in different TCR repertoires (255, 256). Hybrid immunity also results in qualitative differences in T cell immunity (253), including tissue-localized T cells, which are likely important for protective immunity and are elicited only by infection or mucosal antigen exposure (136, 139, 143).

Infections occurring in previously vaccinated subjects (breakthrough infections) are frequently associated with relatively mild symptoms, indicating substantial preservation of protection from severe disease. Breakthrough infections result in robustly increased antibody responses and thus reflect another variation on hybrid immunity (207). T cell responses in breakthrough infections are a complex topic, hindered by the lack of preinfection samples in most cases. Some cases appear to resemble hybrid immunity, while others do not (70). Increased CD4 T cell and CD8 T cell

responses were reported in a cohort of young healthy subjects (257). Two relatively large studies found that at or near onset of the infection, SARS-CoV-2-specific T cell frequencies of breakthrough cases were not different from those of nonbreakthrough vaccinated controls (258, 259). An impressive analysis of over 4,000 epitope-specific TCR sequences demonstrated no evidence for repertoire narrowing from repeated exposure (256). In contrast, when focusing on more serious moderate to fatal cases of COVID-19, patients did not develop proper CD4 and CD8 T cell responses to spike after vaccination (260). Taken together these observations suggest that breakthrough infections are a complex phenomenon, reflecting both the circumstances surrounding reinfection (type of exposure, variants, viral doses) and the immune status of the host (261).

PREEXISTING MEMORY RESPONSES TO SARS-CoV-2 SEQUENCES IN UNEXPOSED DONORS

Early on it was noted that memory T cell reactivity to SARS-CoV-2 epitopes is detected in nonexposed individuals (19). This observation was independently reported by several groups in diverse settings and geographical locations (99, 100, 262, 263). Some of this reactivity was ascribed to memory T cells recognizing human common cold coronavirus (CCC) epitopes with sequence homology to SARS-CoV-2 (264), although potential cross-reactivity of T cell epitopes derived from other viral species was also reported (111, 265, 266).

Numerous studies reported different epitopes associated with different degrees of CCC-SARS-CoV-2 cross-reactivity (28, 53, 82, 114, 267–270). Several additional studies reported cross-reactivity between SARS-CoV-2, SARS-CoV-1, and MERS at the level of T cell responses, consistent with their close phylogenetic relation and the high degree of structural similarity and sequence homology (46, 53, 263). The Kwok and Koelle groups (48) found that the majority of SARS-CoV-2 epitopes have low homology and do not cross-react with SARS-CoV-1, consistent with findings of other large studies (51, 174). Additional studies mapped cross-reactive/conserved epitopes and associated TCRs of potential interest for inclusion in vaccine constructs (43, 45, 48, 267, 271–277). Of note, CD4 T cells from COVID-19 mRNA vaccine recipients recognize a conserved epitope present in diverse coronaviruses (278), including some bat coronaviruses of zoonotic concern.

BIOLOGICAL RELEVANCE OF CROSS-REACTIVE T CELLS

The relevance of CCC cross-reactivity at the T cell level has been debated (279, 280). It was hypothesized that preexisting cross-reactive memory T cells might facilitate faster or stronger responses to infection or vaccination. Studies have now directly shown that preexisting cross-reactive T cells were associated with faster and more durable T cell and antibody responses to COVID-19 mRNA vaccines, providing direct evidence supporting the biological relevance of these cross-reactive memory T cells (174, 281, 282). Additionally, it has been reported that preexisting cross-reactive CD4 T cells result in increased serum but not mucosal antibody responses following BNT162b2 vaccination in elderly people (282).

In the context of infection, several studies reported a positive correlation between detection of cross-reactive CD4 T cells and lower disease severity (82, 281, 283). Separately, Niessl et al. (284) identified cross-reactive resident memory CD8 T cells in unexposed oropharyngeal lymphoid tissue, hypothesizing that these cells might provide a first line of defense. Cross-reactive T cells might provide an initial advantage against COVID-19, even though they might be of lower avidity or only partially overlap the T cell repertoire generated by SARS-CoV-2 infection (27), particularly if the memory T cells are present in the oropharyngeal tissues first infected by SARS-CoV-2. Variations in functional capability of the cross-reactive T cells have been reported (285).

Dowell et al. (134) reported higher levels of cross-reactive T cells in children and hypothesized that this might be a factor in the lower disease susceptibility observed in children. Saletti et al. reported a decrease in OC43- and NL63-specific CD4 T cells in subjects older than 60 years (286). Several studies noted high CCC reactivity in health care workers (287) and then linked this reactivity to possible protection from infections (117, 118). Three studies have reported an association between CCC infection and positive clinical outcomes (288–290), while a third study found no association (291). ORF1a/b regions have been associated with protective outcomes (118), raising the possibility that immunization with a vaccine containing these epitopes might be of value. These clinical outcomes appear to be T cell intrinsic, as CCC antibodies are boosted upon SARS-CoV-2 infection but are generally not associated with COVID-19 protection (291–293).

Positive effects of preexisting immunity are not limited to CCC and in fact are observed in other viral systems such as HIV vaccine (294) and influenza vaccine (295, 296) trials, and memory CD4 or CD8 T cells in an influenza challenge setting (297, 298). Particularly in the absence of neutralizing antibodies, influenza memory CD8 T cells correlated with protection from symptomatic disease (299). Baseline influenza T cell memory predicted lack of symptoms, independent of antibody titers (300).

T CELL RECOGNITION OF SARS-CoV-2 VARIANTS

A first group of variants was identified relatively early in the pandemic, including Alpha, Beta, and Gamma. This was followed by a second group of variants including Delta and Mu. Subsequently, Omicron quickly became dominant in late 2021 and early 2022. These variants commanded the attention of the scientific community, in part due to significant antibody evasion mutations. The question that immediately arose was whether the variant mutations also resulted in escape from memory T cell recognition. Bioinformatic analyses revealed that the vast majority of T cell epitopes were 100% conserved in the variants (51, 271, 301, 302), even though in some particular HLA/epitope combinations a decrease was apparent (303, 304). There was a relative increase in mutated epitopes in Omicron, as expected on the basis of the higher number of mutations associated with this variant, but the mutations were randomly distributed in the spike antigens and were not overrepresented in epitopes, and dominant epitopes were not more frequently mutated than subdominant ones. Bioinformatic analyses were then complemented by direct analysis of CD4 and CD8 T cell reactivity in infection and vaccination. The experiments of Tarke and colleagues (301) showed that more than 80% of the T cell reactivity was preserved at the population level, and in most cases, no decrease at all was apparent. These results were confirmed by several other independent studies in the United States, the Netherlands, and South Africa (271, 305–309). Other populations of interest have been studied with similar findings (199, 218). However, in some particular individual subject/variant combinations, significant decreases were observed (301, 304, 310, 311). Taken together these results indicate that T cell escape at the population level does not drive variant evolution (51).

In conclusion, in the context of variants, the general consensus based on available data is that T cell responses are largely preserved, while neutralizing antibody responses are more drastically affected, particularly with Omicron. This is in agreement with the thousands of SARS-CoV-2 class I and class II T cell epitopes that have been experimentally validated, rendering it exceedingly difficult for the virus to simultaneously mutate enough epitopes to escape T cell recognition at the population level and still retain viral fitness. At the same time, these observations do not preclude that variant-associated mutations might escape certain individual HLA/epitope combinations. This type of T cell escape is well documented in the case of chronic infections such as HIV infection, where the virus has time and opportunity to escape the dominant epitopes recognized in an individual host; but the advantage is lost when a new host expressing different HLAs and

recognizing different epitopes is infected (312). In this light, we note that it has been hypothesized that variants might be generated in the context of prolonged immunosuppression, and therefore it is possible to speculate that variants could bear the imprint of the HLA environment in which they evolved (312–314).

CONCLUDING REMARKS AND FUTURE DIRECTIONS

In conclusion, during the last three years a massive scientific effort has endeavored to understand T cell responses to SARS-CoV-2 infection and vaccination. It is clear that SARS-CoV-2 infection induces vigorous CD4 and CD8 T cell responses that are directed not only against the spike antigen, widely utilized in a majority of vaccination strategies, but also against other antigens, such as N, M, and NSPs. Over 2,000 experimentally verified human T cell SARS-CoV-2 epitopes have been described so far, and in a majority of subjects T cell responses exhibit remarkable breadth.

The role of T cells in modulating disease severity has been much debated. Associations are seen between early T cell responses and less severe COVID-19 outcomes. Compelling evidence in animal models shows that T cell responses are associated with viral control. Data on other respiratory diseases, such as influenza, also implicate T cell responses in reducing disease severity.

SARS-CoV-2 infection is associated with widely variable disease outcomes. Variation in T cell responses may in part contribute to that variability. SARS-CoV-2 T cell responses are modulated by a variety of interrelated variables, such as magnitude and strength of innate immunity and size of the naive memory pool. Preexisting memory T cells recognizing SARS-CoV-2 are also found in many unexposed donors, and studies have demonstrated this cross-reactivity is biologically relevant. In the context of post-acute sequelae of SARS-CoV-2 infection (PASC) (i.e., long COVID), there is a strong need to further pursue T cell biology. Different technologies are being developed to allow measurement of T cell responses in a diagnostic setting, and it is possible that such studies will more conclusively address roles for T cell responses in controlling COVID-19 and PASC.

SARS-CoV-2 vaccines have been remarkably successful in preventing infection and disease. Neutralizing antibodies are a clear correlate of protection, and a large number of studies have also analyzed T cell responses. Tfh cells and GCs are required to develop strong neutralizing antibodies against SARS-CoV-2, and thus CD4 T cell responses are clearly central to the success of the COVID-19 vaccines. For multiple vaccines, T cell memory wanes less rapidly than antibody titers, whereas the circulating T cell frequencies are less readily increased by repeated vaccination or infection. The continued study of these issues is relevant in the context of a potential transition from a pandemic to endemic state, where the general population has reached relatively stable levels of immunity resulting from repeated exposures.

The emergence of SARS-CoV-2 variants has been one of the most significant events in the development of the pandemic. While neutralizing antibody potency is often heavily impacted by variants, T cell recognition of variants has been largely preserved. These observations are consistent with the general trend toward vaccination being associated with decreased efficacy against variant infection but still largely retaining efficacy against severe COVID-19. The remarkable breadth of T cell responses in humans makes it exceedingly difficult for variants to substantially escape T cell recognition at the population level. It is possible that vaccine designs incorporating additional T cell antigens, acting in synergy with antibodies, would be beneficial for preventing severe disease induced by SARS-CoV-2 variants and future coronaviruses.

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