REVIEW ARTICLE | SERIES
https://doi.org/10.1038/s41590-021-01122-w

nature immunology

The T cell immune response against SARS-CoV-2

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The adaptive immune response is a major determinant of the clinical outcome after SARS-CoV-2 infection and underpins vaccine efficacy. T cell responses develop early and correlate with protection but are relatively impaired in severe disease and are associated with intense activation and lymphopenia. A subset of T cells primed against seasonal coronaviruses cross reacts with SARS-CoV-2 and may contribute to clinical protection, particularly in early life. T cell memory encompasses broad recognition of viral proteins, estimated at around 30 epitopes within each individual, and seems to be well sustained so far. This breadth of recognition can limit the impact of individual viral mutations and is likely to underpin protection against severe disease from viral variants, including Omicron. Current COVID-19 vaccines elicit robust T cell responses that likely contribute to remarkable protection against hospitalization or death, and novel or heterologous regimens offer the potential to further enhance cellular responses. T cell immunity plays a central role in the control of SARS-CoV-2 and its importance may have been relatively underestimated thus far.

The cellular immune response has evolved to recognize and control intracellular pathogens and is an essential component of immune defense. T cell immunity developed very early during the evolution of jawed vertebrates[1], and the finding of homologous systems within jawless vertebrates indicates derivation from a common ancestor around 500 million years ago[2]. This underlines the critical importance of cellular immunity for multicellular organisms[3], and therefore it should be no surprise that cellular immunity is critical in the control of a new virus such as SARS-CoV-2.

This Review assesses published studies on the T cell immune response against SARS-CoV-2, with the aim of integrating current understanding. Particular focus is given to the role of cellular immunity in protection against severe acute infection and reinfection, as well as the potential recruitment of cross-reactive human coronavirus (HCoV)-specific T cells into SARS-CoV-2 responses. The generation and clinical importance of T cell responses following COVID-19 vaccination is also discussed, with particular focus on protection against viral variants. Evidence thus far indicates that T cells play a critical role in protection against SARS-CoV-2, and the pace of current progress augurs well for the optimization of future pandemic control.

The coronaviruses comprise a family of enveloped single-stranded positive-sense RNA viruses, with large genomes of 28–34 kb (ref. [4]). Studies of cellular immunity to other HCoVs provide valuable insights into comparable responses against SARS-CoV-2, which emerged in 2019. There are four circulating seasonal 'common cold' HCoVs, which comprise two Betacoronaviruses, OC43 and HKU-1, as well as the Alphacoronaviruses 293E and NL63. These are widely prevalent, with previous exposure to each virus seen in >90% of adults[5]. Antibody responses against HCoVs are not well maintained, and reinfections are common within 12 months[6]. T cell responses against HCoVs are generated but are of relatively low magnitude, and their longevity is uncertain, with low frequency in older people[7]. SARS-CoV-1 offers a more encouraging picture. Although antibody and B cell responses are relatively short lived and frequently became undetectable within 4 years[8,9], T cell responses can be elicited after 17 years[10]. T cell responses to Middle Eastern respiratory virus (MERS) are also of interest and appear to be more robust and sustained than humoral immunity[11]. Recent demonstration of MERS-specific cellular responses without seroconversion in abattoir workers in Nigeria supports the concept of cellular sensitization without seroconversion[12]. Together, these data argue for the central importance of cellular immunity in the control of HCoV infections.

The failure of HCoV-specific antibody and cellular responses to provide sterilizing immunity has led to concern that protective immunity against SARS-CoV-2 will also be short lived. Information at the current time provides a somewhat mixed picture. Reinfection with SARS-CoV-2 does occur, but previous infection provides protection of around 87% at 6 months[13] with a stable profile up to at least 10 months[14]. The emergence of the highly infectious Omicron viral variant has greatly increased the prevalence of breakthrough infection, but the observation that the great majority of T cell immune responses are retained against Omicron is likely to contribute to the attenuated clinical severity.

Cellular immune responses against SARS-CoV-2 during acute infection

Adaptive immune responses are needed to control and eliminate SARS-CoV-2 infection, and there is intense interest in the relative importance of cellular immunity during this period. Evidence from SARS-CoV-1 and MERS indicates that T cells may be the major mediators of disease control[11], and in SARS-CoV-1 infection, high antibody levels have been associated with increased inflammation and impaired clinical outcome[15].

The magnitude of the initial viral load[16] and the efficacy of the innate immune response, particularly that mediated by type I interferons[17,18], seem to be critical in setting the platform for both the subsequent adaptive response and the clinical outcome. Indeed, both genetic factors and acquired factors have clearly demonstrated the critical role of effective interferon signaling in acute infection[19,20]. Severe clinical outcomes are characterized by a slow decline in viral load and early and sustained inflammation with elevated interferon (IFN)-α, TNF and IFN-γ[21] (Fig. 1).

Notwithstanding the importance of innate responses[22], coordinated cellular immunity is also essential in disease control[23]. Early development of a cytotoxic $CD8^+$ T cell response, typically observed within 7 days of symptoms and peaking at 14 days, is correlated with effective viral clearance[24] and mild disease[25] and is in line with similar kinetics for humoral responses[26]. Of note, some of this response may arise from bystander $CD8^+$ T cells, which are not directly virus specific but express an $NKG2D^+IL\text{-}7R^+$ phenotype and contribute to disease control in other settings[25,27]. Despite this apparent robust cellular response in most people, up to 20% of people with

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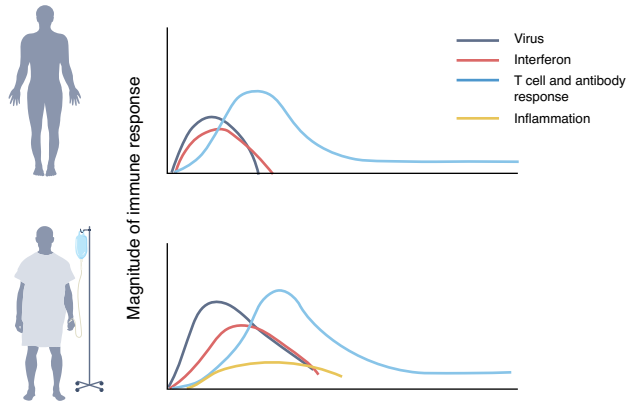

Fig. 1 | Representation of immune correlates in relation to clinical severity during primary SARS-CoV-2 infection. Effective clinical control of primary SARS-CoV-2 infection is associated with early and robust interferon and adaptive immune responses, which effectively control viral load. A delayed, inadequate, and prolonged interferon response seems to be associated with slowed and elevated cellular activation, with early inflammation and a poor clinical outcome.

COVID-19 display poor adaptive immunity and may potentially represent those who benefit from early antibody therapy[28].

A profound lymphocytopenia is seen in the blood of many individuals with acute SARS-CoV-2 and is correlated with severe clinical outcome[29]. This leads to a pattern of 'coexisting suppression and activation', with peripheral loss of up to 80% of T cells[30,31] concurrently with intense proliferation of ~20% of the CD8$^+$ T cell pool. The mechanisms that underlie lymphocytopenia are unclear but could reflect impaired lymphocyte proliferation, apoptosis[24], or extravasation into tissue. Lymphopenia is also seen in several other infections[32,33], although it seems to be more rapid, profound, and long-lasting in the setting of COVID-19. Resolution of lymphopenia correlates with recovery[34] but can take several weeks.

The functional capacity of the cellular response is also a key determinant of clinical outcome. Effective viral control is associated with a type 1 CD4$^+$ phenotype; a type 2 profile is often seen in those with severe disease[24,35]. High expression levels of effector molecules by CD8$^+$ T cells in acute COVID-19 are associated with improved clinical outcome[36]. However, excessive activation may be detrimental, and although polyfunctionality peaks in moderate disease[36], excessively high levels of T cell activation are associated with poor clinical outcome[37]. Expression of markers of potential exhaustion, such as PD-1 and Tim-3, are associated with disease progression[34], although this may not necessarily reflect functional exhaustion[38] but instead ongoing activation.

An emerging picture is that people who develop severe disease display early onset of inflammation, together with a delayed and relatively excessive adaptive immune response. The reason why some people develop this profile is not clear, although delayed and suboptimal activation of the type I interferon pathway may be critical (Fig. 1). In addition, co-morbid conditions and aging, which are major clinical determinants of poor outcome, may act to suppress the development of adaptive T cell responses[39,40].

The extreme pattern of T cell activation in acute SARS-CoV-2 has led to concern that the cellular response may contribute to immunopathology. Virus-specific T cell responses in asymptomatic infection are characterized by balanced production of IL-10 and inflammatory cytokines, while symptomatic disease is characterized by more polarized production of inflammatory mediators[41,42]. The relative importance of SARS-CoV-2-specific regulatory T cells in relation to disease course is unclear at this stage[43], but the clinical outcome of severe COVID-19 is dominated by systemic inflammation and severe pneumonitis, and virus-specific T cell responses have been shown to contribute to tissue damage in other respiratory infections[44]. Some post-mortem studies have indicated that there is lymphocytic infiltration within tissue[45,46], although profiles are very heterogeneous. High levels of viral load are typically seen within tissue[47] and may drive exuberant immune responses, but at this stage it is unclear to what extent the beneficial action of drugs such as dexamethasone[48] and IL-6R antagonists[49] is mediated through suppression of T cell activation.

Specificity, phenotype, and function of SARS-CoV-2-specific T cell responses

Despite the considerable mortality rate of primary SARS-CoV-2 infection, most people do survive and eradicate the virus. SARS-CoV-2-specific T cells develop in almost everyone, and a range of studies are now defining the properties and clinical importance of this response. Assessment of global virus-specific T cell responses within an individual is more complex than investigation of humoral immunity, owing to the complexity of studying cellular responses against peptides presented through multiple HLA alleles. However, much progress has been made, and the curation and analysis of cellular responses against SARS-CoV-2 is likely to soon exceed those documented against any other infection.

T cell responses against SARS-CoV-2 were identified rapidly following release of the SARS-CoV-2 sequence. Peng and colleagues used ELISpot technology to assess the breadth of T cell immune responses and found them to be stronger in individuals with more-severe initial infection[50]. The subsequent use of peptide pools covering the entire viral proteome allowed identification of T cell responses against almost all proteins, the magnitude of which correlated with the level of protein expression from each gene[51,52]. The magnitude of CD4$^+$ and CD8$^+$ T cell responses is highly correlated against almost all proteins, although some, such as nsp12, induce weak CD8$^+$ T cell responses and likely reflect differential mechanisms of antigen presentation[51]. Spike-specific T cell responses are CD4$^+$ dominated and are likely to support antibody generation, with follicular helper T cells correlating with humoral immunity in the memory phase[53–55].

SARS-CoV-2 has a very large 30-kb messenger RNA (mRNA) genome, so it is not surprising that it encodes many T cell epitopes. Most studies have focused on T cell responses to structural proteins, such as spike, membrane, and nucleocapsid, but many other regions, such as ORF3, nsp3, nsp4, and nsp12, encode important epitopes. Indeed, over 1,400 potential epitopes have been identified so far[56,57]. Genomic regions of immunodominance are emerging, as are defined peptide epitopes that are commonly shared between donors[58], including those within the receptor-binding domain (RBD)[59]. Moreover, immunodominant peptides may also be derived from out-of-frame open reading frame sequences that are not captured in current vaccine regimens[60,61].

A notable recent observation was the finding that CD8$^+$ T cell responses against the $NP_{105–113}$ epitope restricted by B*07:02 demonstrate strong anti-viral activity and correlate with protection from severe disease[62].

The phenotype of the SARS-CoV-2-specific T cell memory response is attracting considerable interest. CD4$^+$ cells are characterized by a polyfunctional profile[63] with high levels of IL-2, although IFN-γ production is somewhat lower than has been observed against other respiratory viruses[38] (Fig. 2). Single-cell transcriptomic analysis at 4 weeks after infection shows highly expanded cytotoxic populations of both CD8$^+$ T cells and CD4$^+$ T cells, although cytotoxic CD4$^+$ subsets are not a major feature of the memory response. CD4$^+$ responses are somewhat larger than the CD8$^+$ pool[64] and may even increase in frequency over time[65], potentially reflecting antigen persistence[66]. A SARS-CoV-2-specific stem cell memory pool does develop[38,67], and most CD4$^+$ cells express a central memory profile[63],

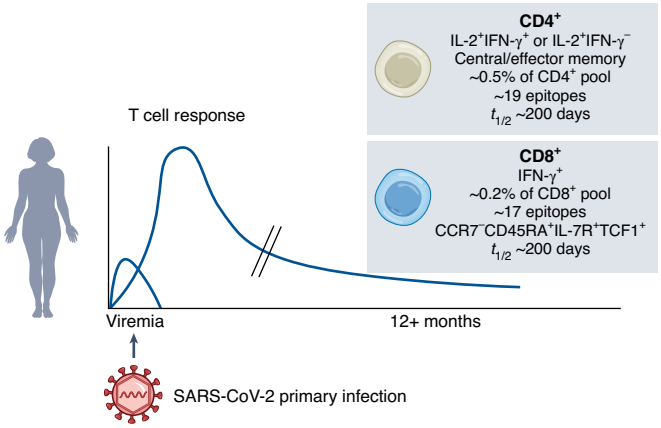

Fig. 2 | The profile of T cell immune memory to SARS-CoV-2 following clearance of primary infection. Memory T cell responses are maintained within the first 12 months following clearance of infection by CD4+ T cell populations and CD8+ T cell populations, which comprise ~0.5% and ~0.2% of the repertoire and target at least 19 epitopes and 17 epitopes, respectively. $t_{1/2}$, half-life.

both of which augur well for longevity of responses. Indeed, there is hope that SARS-CoV-2-specific T cells will be maintained for many years, although this may depend on the clinical severity of the initial infection[68]. Robust immunity is certainly maintained by 6 months[69] and beyond[67], while prospective studies show some refocusing of T cell specificity over time[65] and an estimated half-life of around 200 days for virus-specific cells[63]. Long-lived T cell responses are characterized by a CD45RA+ effector-memory phenotype and display a characteristic interferon transcriptome[70].

The magnitude of the SARS-CoV-2-specific CD4+ and CD8+ memory T cell response is typically around 0.5% and 0.2% of the repertoire, respectively[63], although a characteristic feature is heterogeneity between donors. The breadth of response within individual donors has been estimated at approximately 19 and 17 epitope-specific responses in most people[51] (Fig. 2). This provides reassurance that viral mutation is unlikely to be sufficient to facilitate evasion from T cell recognition.

Most T cells within the body are present as resident memory cells within tissue, and the development of sentinel virus-specific memory pools at airway sites is likely to be important in protection against reinfection. The number of SARS-CoV-2-specific resident memory T cells in the lungs correlates with clinical protection[71], and as they can be detected for at least 10 months after infection, it is likely that they play an important role in limiting the severity of reinfection[42]. The induction of these cells following vaccination in animal models is also encouraging[72].

T cell cross-recognition against other HCoVs

As indicated above, there are six extant HCoVs, and residual immune responses to SARS-CoV-1 remain in some people. These viruses show moderate amino acid conservation with SARS-CoV-2, which is particularly marked for SARS-CoV-1 and MERS, although somewhat less than is seen for some internal proteins of influenza subtypes. Thus, T cell epitopes are likely to be shared between viruses, and this cross-reactivity may be important in clinical protection[73]. Functional cross-reactive responses have indeed been observed[10,74,75], although this has not been seen in all reports[50]. Some differences may relate to technical assays, as approaches such as activation-induced markers or proliferation assays display higher sensitivity than does ELISpot analysis[76]. The molecular basis for cross-reactive recognition of SARS-CoV-2 and HCoV peptides by individual T cell clones is now starting to be defined[77]. In this context, it is important that studies extend beyond the use of peptide stimulation to include recognition of virus-infected cells, as presentation of apparently cross-reactive peptides can vary between different coronaviruses[77]. Indeed, it may be somewhat premature to consider candidate peptide targets as genuine 'epitopes', where these have been identified through use of high peptide concentration in vitro, until confirmed with physiological assays[78].

It is noteworthy that children and young adults show higher levels of antibody cross-reactivity between HCoVs and SARS-CoV-2, potentially as a result of more recent HCoV infection, and antibodies that can neutralize SARS-CoV-2 are detectable in some children prior to any exposure to SARS-CoV-2 (ref. [79]). Cross-reactive T cell responses are also seen in young children[80], and both the humoral responses and cellular responses are focused against the spike 2 domain, which is highly conserved between the different coronaviruses. It is not clear why there may be such an age-dependent influence on cross-reactive adaptive immunity, but this could relate to strong immune activation from primary HCoV infections in children. Alternatively, children may be evolutionarily programmed to develop more cross-reactive immune responses, as was previously observed in 'back-boosting' of influenza immunity[81], and it is tempting to think this may be related to the rare but severe complication of pediatric multisystem inflammatory syndrome after SARS-CoV-2 infection in young children.

There remains debate as to the clinical importance of cross-reactive T cell responses in the control of SARS-CoV-2 (ref. [74]), although some support has come from animal models of SARS-CoV-1 infection[82,83]. Individuals with robust HCoV-specific T cells may potentially be primed for superior protective cellular immunity following exposure to SARS-CoV-2, and recent infection with an HCoV appears to be associated with a better clinical outcome after SARS-CoV-2 infection[84].

Precedent for this model does exist in influenza, for which pre-existing cytotoxic CD4+ T cells enhance homotypic and heterotypic viral clearance in human challenge models, with strong T cell responses observed as early as at day 7, prior to detection of antibody responses[85]. In addition, during the H1N1 pandemic, higher frequencies of pre-existing CD8+ T cells were correlated with less-severe illness[86]. This idea is further supported by the unexpected observation that HCoV-specific T cells are largely absent from the T cell repertoire in older people, a group known to be at high risk of severe infection[7]. Therefore, the pre-existing HCoV-specific cellular repertoire might indeed be usefully incorporated into the SARS-CoV-2-specific immune response, although thus far there is little evidence that this is expanded selectively over de novo clones[65]. Indeed, the most immunodominant CD8+ T cell response known so far is the N105 peptide presented by HLA-B*07:02, and this arises from a high frequency of T cells within the naive T cell repertoire that are able to recognize N105, rather than from previously HCoV-primed cells[87].

Some arguments against clinical protection from cross-reactive immunity have also been developed. HCoV-specific T cells are often of low avidity against SARS-CoV-2 peptides[88,89], and a de novo SARS-CoV-2-specific response may be required for effective control. Indeed, an excessive reliance on the cross-reactive pool owing to reduced diversity of available naive T cells may actually be counterproductive and contribute to the impaired clinical outcomes seen in older people[88]. Thus, an important area of future research is mapping the pre-existing cross-reactive T cell repertoire and assessing to what extent this becomes incorporated into the total SARS-CoV-2-specific immune response after infection or vaccination (Fig. 3).

T cell recognition of SARS-CoV-2 viral variants of concern

SARS-CoV-2 has a large polycistronic RNA genome of approximately 30 kb that encodes 14 open reading frames, some of which are overlapping. Given the large size of this genome, the virus has

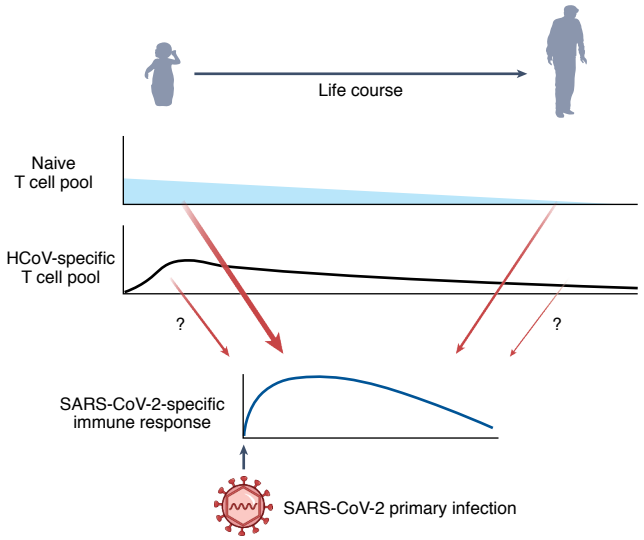

Fig. 3 | The potential contribution of HCoV-specific T cells to the cellular immune control of primary SARS-CoV-2 infection. The size of the naive T cell repertoire decreases across the life course, and the magnitude of the memory T cell pool against seasonal HCoVs also seems to decrease. Following primary infection, the SARS-CoV-2-specific T cell response comprises de novo effector T cell clones derived from the naive repertoire and may potentially also include HCoV-specific cells that are cross-reactive with SARS-CoV-2.

evolved an RNA proofreading mechanism during replication, and there was hope that this would provide relative protection from the rapid development of viral mutations[90]. Despite this, a wide range of mutations have been observed within the SARS-CoV-2 genome over the past 18 months, and many of these have led to the development of variants with novel properties[91]. Several have been defined as 'variants of concern' (VOCs) on the basis of their capacity for increased transmission or relative immune escape, and mutations are frequently focused within the RBD of the spike protein, which is the target for many neutralizing antibodies[92]. Therefore, antibody neutralization of viral VOCs can be severely compromised.

The potential importance of viral mutation in driving escape from T cell control is a topic of considerable debate. Currently, it is unlikely that these variants will be able to evade a considerable proportion of the SARS-CoV-2-specific T cell response. Single point mutations can indeed abolish functional responses from individual T cell clones, but within each host, and across the population, it is unlikely that this will substantially abolish cellular immune control[93]. The 'digital' nature of cellular recognition is such that synonymous amino acid changes would be required across the breadth of the cellular recognition portfolio, and it has been estimated that <30% of cellular responses will be lost in relation to cellular recognition of typical VOCs[94,95]. Nevertheless, a recent study has shown spike mutations can lead to loss of T cell recognition within epitopes restricted by common HLA alleles, such as A*03:01, A*11:01, and A*01:01 (ref. [96]) (Fig. 4), This is potentially important, given that population immunity may not yet be sufficient to drive strong T cell selection comparable to that which has been seen for H3N2 influenza virus[97]. T cell recognition also seems to be broadly cross-reactive against the Omicron variant, although the large number of mutations within spike will inactivate presentation or recognition of some epitopes. More convincing evidence of T cell escape will likely require evidence of intra-host evolution. At the current time, potential mechanisms by which viral proteins or RNA may act to directly suppress antigen presentation are unclear, although ORF8 can downregulate expression of HLA class I proteins[98].

Evidence for a protective role of T cell immunity in the control of SARS-CoV-2 infection

Perhaps the most important question in relation to cellular immunity against SARS-CoV-2 is its role in providing clinical protection. Increasing evidence now supports a potential role in both preventing initial infection and, more importantly, limiting the extent of disease following infection.

Animal models have played a valuable role in delineating the importance of adaptive immune responses in SARS-CoV-2 infection. The non-human primate macaque model has been particularly important, and although neutralizing antibodies are protective against viral challenge, the $CD8^+$ T cell response contributes to protection in the setting of low or waning antibody levels[99]. $CD4^+$ T cell adoptive transfer was previously shown to be protective against MERS and SARS-CoV-1 (ref. [100]).

In human infection, antibody responses are generally considered to provide protection against initial infection, and the induction of virus-specific neutralizing antibodies within the airways is considered the most likely predictor of future protection following natural infection or vaccination. However, accumulating evidence suggests that cellular responses may also play an important role in preventing initial productive infection. Indeed, an important concept that has developed during the COVID-19 pandemic is that of 'cellular sensitization without seroconversion'. The presence of antibodies against a pathogen is typically regarded as a 'gold standard' for previous infection, but many individuals with substantial exposure to SARS-CoV-2, such as healthcare workers, demonstrate virus-specific cellular responses without evidence of virus-specific antibodies[101–103]. This phenomenon has been described previously in people heavily exposed to human immunodeficiency virus[104] and indicates a potential role for the cellular immune system in clearing infection before it is fully established. Proteins expressed within the first 3 hours after infection dominate epitope responses[60], and the replication complex, which is one of the first proteins to be produced within the viral life cycle, is also highly conserved between HCoVs. In particular, cellular responses against RNA polymerase represent a large proportion of such cellular sensitization and may represent important candidates for future vaccine studies[105].

Once infection is established, the adaptive immune response is required for viral clearance. Antibodies clearly play a critical role in viral neutralization, but there is evidence that the virus may spread by cell-to-cell contact and that this dissemination is resistant to antibody neutralization[106]. This mechanism has been observed with several other viruses[107] and suggests that T cell immunity may be essential for viral clearance.

Further evidence for the importance of cellular responses comes from studies of infection in people with inherited or acquired impairment of antibody responses[108], and T cell responses have been associated with protection in people with cancer undergoing therapy with B cell–depleting agents, such as anti-CD20 antibody[109].

SARS-CoV-2-specific T cell responses following COVID-19 vaccination

The COVID-19 pandemic might be considered to be divided into two major phases: before and after 9 November 2020, the date that Pfizer and BioNTech announced results from the phase 3 study of the BNT162b2 mRNA vaccine[110]. This showed >90% protection against COVID-19 and transformed approaches to control of the pandemic. A wide range of vaccines have been developed since that time, and many show very high levels of protection, with particularly marked efficacy in relation to severe disease and death. In order to optimize the delivery and efficacy of these vaccines, it is now essential that the critical determinants of cellular T cell responses within vaccine-mediated protection are accurately defined.

Most current vaccines rely on delivery of the spike protein, and spike-specific cellular responses are measured in most vaccine

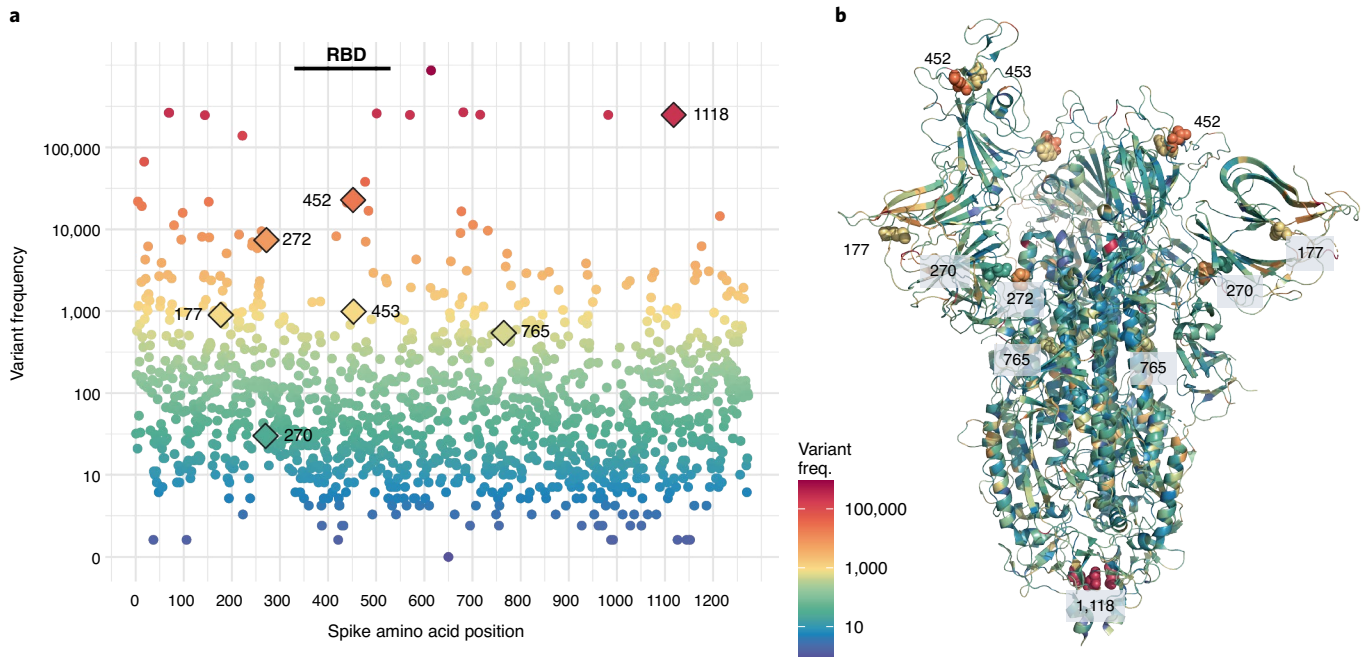

Fig. 4 | Mutations known to impact T cell recognition are not focused within the RBD. Representation of frequency and structural context of amino acid substitutions known to affect T cell epitope recognition. **a**, Global frequency of amino acid variants relative to the Wuhan-Hu-1 reference sequence, including substitutions and deletions, at each amino acid position of the spike protein. Variants were identified using CoV-GLUE[129], which filters out GISAID sequences identified as low quality or as being from non-human hosts (sequences retrieved from GISAID database on 6 April 2021 (ref. [130])). Diamonds highlight the positions of amino acid residues 177, 270, 272, 452, 453, 765, and 1118, where substitutions affect recognition of T cell epitopes[96]. Points are colored to show variant frequency according to key. The location of the RBD (residues 330–530) is indicated. **b**, Structure of the spike protein ectodomain in open form[131] (RCSB Protein Data Bank ID: 6ZGG) in cartoon representation, with residues colored to show the global frequency of amino acid variants. Spheres highlight the locations of residues 177, 270, 272, 452, 453, 765, and 1118. Figure courtesy of W. Harvey, D. Wright, D. L. Robertson (MRC-University of Glasgow Centre for Virus Research), and A. Carabelli (University of Cambridge).

registration studies, albeit in a proportion of participants[111]. Interestingly, a protective clinical effect is seen within 11 days after first vaccination, and a robust $CD8^+$ T cell response can be seen in this early period, suggesting that it may underpin, or at least contribute to, this observation[112]. T cell responses will also be needed to support the generation and maintenance of high-affinity antibodies, and dual vaccination with BNT162b2 leads to reliable induction of virus-specific $CD4^+$ T cell responses[113]. These $CD4^+$ responses exhibit a T_H1 profile and are typically detectable by day 8 after priming, peak soon after vaccine boost, and then fall to pre-boost levels after 4 months[114].

Importantly, T cell responses after dual vaccination are of similar magnitude to those seen after natural infection, although they seem to be somewhat more differentiated. This is reassuring, although a key question now relates to the longevity of such responses. Antibody waning after vaccination remains a concern, but T stem cell memory subsets are induced after vaccination, and there is hope that cellular immunity will remain more robust.

It is interesting to speculate on the relative contribution of cellular responses in the clinical protection mediated by vaccines. One characteristic feature of COVID-19 vaccines is their enhanced ability to protect from severe disease in comparison to asymptomatic or mild infection. This may indicate some limitation in the ability of antibodies to prevent initial infection, and it is tempting to speculate that cellular responses provide the underpinning control of serious tissue damage. Indeed, although many viral VOCs can strongly evade humoral immunity, cellular responses induced by vaccines show strong cross-protection against VOCs and support the concept that cellular responses contribute substantially to disease control[114].

The magnitude of spike-specific T cell induction varies according to vaccine subtype, with the adenovirus-based platforms generating somewhat stronger responses in some studies[115,116], while mRNA platforms develop higher antibody titers. This has led to interest in the use of heterologous vaccine platforms[117,118], although short-term vaccine side effects are somewhat higher with this approach[119]. New formulations, including peptide formulations, are also being assessed[120].

Vaccine-induced cellular responses are markedly enhanced in donors with a history of prior natural infection and typically peak after only one vaccine[121]. The qualitative response may also be modified with evidence for increased tissue homing properties in those with previous natural infection[122]. These observations are pertinent to discussions on increasing the breadth of vaccine immunogens to include proteins, such as nucleoprotein or RNA polymerase, that broaden the magnitude and quality of cellular protection. Vaccines that support development of intranasal cellular responses may also enhance clinical protection in the longer term[123].

SARS-CoV-2-specific T cell responses as an immune correlate of protection

As the prevalence of vaccination and natural infection increases across the world, there is increasing interest in developing approaches that predict individual risk of primary or reinfection. Such a 'personalized' approach to risk management depends on the development of accurate immune correlates of protection[124]. Almost all such studies have focused on the magnitude of the spike-specific antibody response or neutralizing titer[125,126]. In contrast, much less attention has been given to the magnitude or functional profile of cellular immune responses.

One major reason has been the much greater complexity and cost of measuring cellular immune responses. Effective correlates will require investigation of large population cohorts with accurate cellular assays that allow correlation with both asymptomatic infection and symptomatic infection. Such approaches are now being undertaken and should help to define the relationship between humoral immunity and cellular immunity in long-term protection. People who have developed poor T cell responses after vaccination may benefit from optimized vaccine formulations, potentially including those that comprise defined immunogenic peptide epitopes[127].

In order to apply this information at a population level, the development of rapid, high-throughput cellular assay systems will likely be needed. Most studies currently use techniques such as ELISpot[50] or intracellular cytokine staining[63], which, although accurate, sensitive, and well-established, remain somewhat time-consuming and expensive. Whole-blood peptide-stimulation assays and T cell receptor sequencing systems[128] are also now being developed, and one of the legacies of the current pandemic will be increased impetus for the development of sophisticated cellular analyses that can be applied to a range of studies within human immunology.

Concluding remarks

A wide range of studies have shown that the T cell response is a critical component of immune protection against SARS-CoV-2. This should come as no surprise. Cellular immunity is essential for the protection of multicellular organisms, and coronaviruses have co-existed with *Homo sapiens* over long periods of time. Evidence now suggests that SARS-CoV-2-specific T cell responses are essential for viral clearance, may prevent infection without seroconversion, provide robust memory, and mediate recognition of viral variants. They are also elicited after vaccination, where they may underpin outstanding protection against severe infection and death. Antibody responses are clearly also highly effective in clinical protection, and their analysis has been facilitated by relative ease of detection and assessment. Cellular responses remain more difficult to study, but this challenge is now being addressed during the COVID-19 pandemic.

Despite tremendous progress, there remain many critical questions that need to be resolved about T cell immunity to SARS-CoV-2. The features of an optimal coordinated cellular response at primary infection and the relative recruitment from the pre-existing HCoV-specific repertoire across the life course remain uncertain. Detailed characterization of $CD4^+$ and $CD8^+$ T cell immune memory and its contribution as a correlate of future protection requires resolution. In addition, the ability of different vaccine regimes to elicit optimal cellular responses, and how these will contribute to protection against the emergence of viral variants such as Omicron, are critical questions for control of the pandemic. It is now timely to deepen our understanding of T cell immunity against this novel viral threat and also to exploit this innovation to uncover the full importance of cellular immunity in many other areas of human disease.

Received: 25 August 2021; Accepted: 10 December 2021;
Published online: 1 February 2022

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Competing interests

The author declares no competing interests.

Additional information

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Peer review information *Nature Immunology* thanks Tao Dong and Jacob Kohlmeier for their contribution to the peer review of this work. Jamie D. K. Wilson was the primary editor on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.

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