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Review

SARS-CoV-2-specific T cells in the changing landscape of the COVID-19 pandemic

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SUMMARY

Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, multiple severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants with increasing ability to evade neutralizing antibodies have emerged. Thus, earlier interest in defining the correlates of protection from infection, mainly mediated by humoral immunity, has shifted to correlates of protection from disease, which require a more comprehensive analysis of both humoral and cellular immunity. In this review, we summarized the evidence that supports the role of SARS-CoV-2-specific T cells induced by infection, by vaccination or by their combination (defined as hybrid immunity) in disease protection. We then analyzed the different epidemiological and virological variables that can modify the magnitude, function, and anatomical localization of SARS-CoV-2-specific T cells and their influence in the possible ability of T cells to protect the host from severe COVID-19 development.

INTRODUCTION

The epidemiological, virological, and immunological landscape of coronavirus disease 2019 (COVID-19) has evolved substantially since the onset of the pandemic. The ancestral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lineage that triggered the initial pandemic (Zhou et al., 2020) has since been substituted by diverging lineages (at the moment of publication, Omicron BA.5) (Dorp et al., 2021; Fan et al., 2022), and most of the global population is no longer immunologically naive due to prior infection and/or vaccination (Krause et al., 2021). Instead, we are confronted with a mosaic of “hybrid immune situations” that can no longer be classified simply as cases of viral infection in naive or convalescent individuals. Adaptive immune priming has largely been obtained from viruses or vaccines now antigenically distinct from the circulating viral lineages, with parenteral vaccinations inducing an immune response that is not identical to natural infection in terms of localization, antigenic breadth, or function.

The scientific community has responded quickly to the pandemic by generating an unprecedented body of scientific work that has interrogated many different aspects of host-virus interactions. The characteristics of virus-specific T cell responses induced during SARS-CoV-2 infection and vaccination have largely been analyzed and summarized in several comprehensive reviews (Altmann and Boyton, 2020; Bertoletti et al., 2021a; Kedzierska and Thomas, 2022; Moss, 2022; Niessl et al., 2021a; Sette and Crotty, 2021). Such analyses were, however, focused more on determining the presence and persistence of T cell responses to infection or vaccination in naive subjects. In this review, we will primarily discuss how different variables (Figure 1) can influence the ability of T cells to protect the host from severe COVID-19 development and how these variables have changed in relation to the evolving epidemiological, virological, and immunological landscape.

SARS-CoV-2-SPECIFIC T CELLS: A CORRELATE OF PROTECTION FROM DISEASE SEVERITY?

T cells are a highly specialized component of the human immune system. During viral infection, two populations of T cells, CD4⁺ and CD8⁺, perform non-redundant immunological functions that complement both the ability of the innate immunity to contain viral replication and the ability of antibodies to prevent infection (Sette and Crotty, 2021). Utilizing their specific T cell receptors (TCRs), CD8 T cells detect the host cells that harbor replicating viruses through recognition of viral sequences (epitopes) derived from the processing of endogenously synthesized viral proteins that are presented by major histocompatibility complex class I molecules on the surface of the cells. Recognition is followed, if the CD8⁺ T cells are functionally fit, by the direct lysis of the infected cells and the release of cytokines (interferon [IFN]- γ and tumor necrosis factor [TNF]- α) that have direct antiviral effects.

CD4⁺ T cells can recognize and directly lyse virus-infected cells as well (Heller et al., 2006), but they are mainly activated by epitopes derived from the processing of viral proteins internalized by uninfected professional antigen-presenting cells (mainly dendritic cells or other myeloid-lineage cells) and presented by the MHC class II molecules. Naive CD4⁺ T cells can develop into specialized subsets (Th1, Th2, Th17, Treg, and T follicular helper [Tfh] cells) characterized by distinct gene expression programs (O’Shea and Paul, 2010), with SARS-CoV-2 infection mainly supporting the expansion of Tfh and Th1 helper CD4⁺ T cells (Braun et al., 2020b; Thevarajan et al., 2020; Weiskopf et al., 2020). Tfh cells are primarily required to help B cell proliferation and production of high-affinity antibodies within the germinal center of secondary lymphoid organs (Crotty, 2011), but they are also involved in sustaining CD8⁺ T cell function (Zander et al., 2022). In contrast, Th1 cells are not involved in B cell maturation



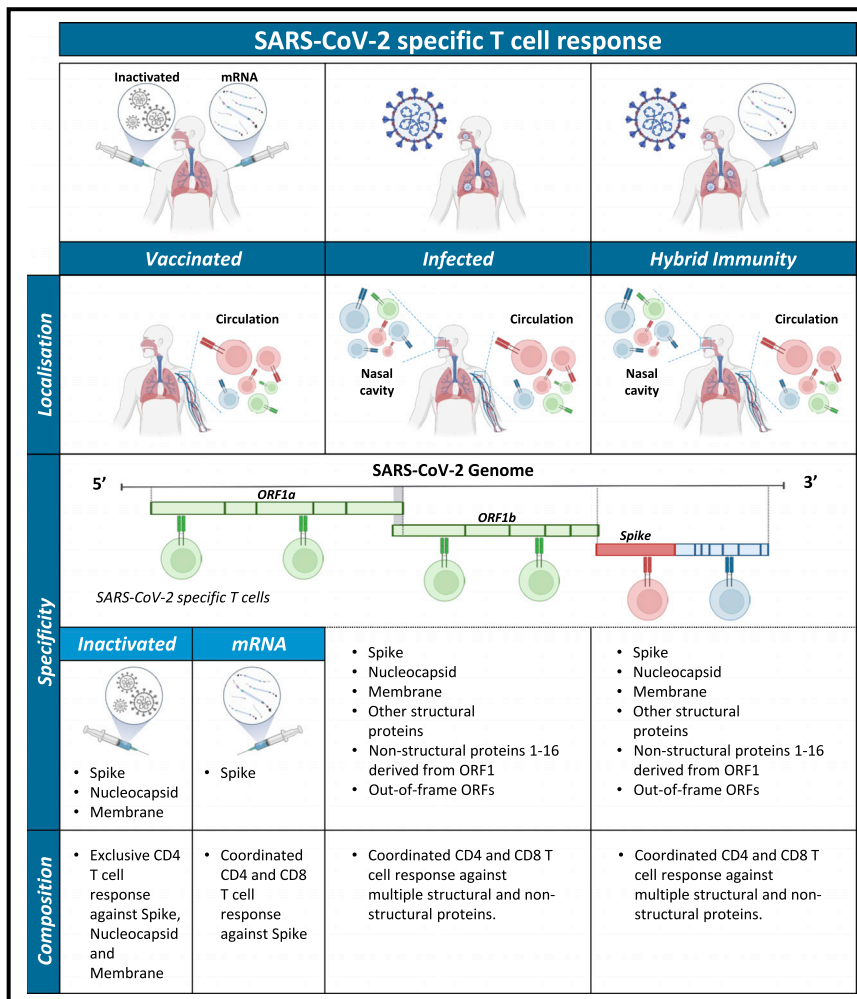


Figure 1. Localization, specificity, and composition of SARS-CoV-2-specific T cells in vaccinated, infected, and individuals with hybrid immunity

This illustration summarizes the key features of SARS-CoV-2-specific T cell responses observed in individuals who were vaccinated, infected, or developed hybrid immunity after breakthrough infection post-vaccination. The anatomical niche(s) occupied by the SARS-CoV-2 T cells (localization), the viral antigen(s) targeted by the indicated T cells (specificity), and the CD8⁺ and CD4⁺ T cell subsets induced in each scenario (composition) were described.

quantities of SARS-CoV-2-specific memory T cells in individuals who experienced more severe disease (Peng et al., 2020; Zhang et al., 2021a; Zuo et al., 2021). Links were only established between the ability to rapidly mount a coordinated humoral and multi-specific T cell response with protection from severe disease by using more comprehensive analyses of the level of humoral and cellular antiviral immunity in groups of patients with varying infection outcomes. For example, by comparing adult patient cohorts with either mild or severe COVID-19, the research groups of Sette and Crotty showed that the ability to mount a coordinated immune response comprising SARS-CoV-2 humoral and cellular immunity was associated with recovery from infection without severe pathology (Möderbacher et al., 2020). Kinetic studies quantifying SARS-CoV-2-specific T cell and antibody responses

and instead support cellular and innate immunity against pathogens (McKinstry et al., 2012; Strutt et al., 2010) and have been shown to be essential for control of herpesvirus infection (Heller et al., 2006). The timing of IFN- α production after viral infection seems to critically regulate antiviral CD4⁺ T cell polarization. Viruses that induce an early IFN- α response (<24 h from infection) can drive a marked Tfh polarization through induction of interleukin (IL)-6 production in dendritic cells (De Giovanni et al., 2020).

Merely months after the onset of the COVID-19 pandemic, and the characterization of SARS-CoV-2 as its etiological agent, several groups around the world collectively demonstrated that T cell subpopulations (effector CD8⁺ T cells and Tfh and Th1 CD4⁺ T cells) specific for various SARS-CoV-2 proteins could be detected both in COVID-19 convalescents (Braun et al., 2020b; Grifoni et al., 2020; Le Bert et al., 2020; Schulien et al., 2021; Thevarajan et al., 2020; Weiskopf et al., 2020) as well as in asymptotically infected individuals who did not seroconvert (Le Bert et al., 2021a; Reynolds et al., 2020; Sekine et al., 2020). Relationships between the presence of SARS-CoV-2-specific T cells (CD4⁺ and CD8⁺) and protection from severe disease were unclear, however: initial studies often detected higher

over the course of acute infection in naive individuals detected a rapid expansion of IFN- γ -producing T cells specific for different structural and non-structural SARS-CoV-2 proteins including spike (S), membrane (M), nucleocapsid protein (NP), and ORF7/8 in patients who experienced rapidly controlled SARS-CoV-2 replication without severe disease. In contrast, patients with prolonged infection and severe COVID-19 mounted robust antibody responses but had undetectable circulating SARS-CoV-2-specific T cells (Tan et al., 2021a). These initial studies that supported the idea that T cells offer an important contribution to protection against COVID-19, i.e., disease development, were confirmed subsequently in larger longitudinal studies performed in mild/severe (Tarke et al., 2022a) or asymptomatic or pauci-symptomatic patients (Chandran et al., 2022). Finally, increased frequencies of T cells specific for polymerase (NSP-12) (Swadling et al., 2021) or other SARS-CoV-2 proteins (Kundu et al., 2022) in individuals who successfully aborted infection (highly exposed individuals who remain seronegative and PCR negative for SARS-CoV-2) suggests that a rapid deployment of virus-specific cellular immunity suppresses viral replication. These correlative studies in patients complemented mechanistic studies in animal models: a substantial reduction in

the ability of antibodies to control viral infection was demonstrated in CD8⁺ T cell-depleted SARS-CoV-2 convalescent macaques (McMahan et al., 2021); a mouse model of SARS-CoV-2 showed the importance of T cell responses in controlling lung pathology (Zhuang et al., 2021).

The impact of COVID-19 vaccine-induced T cell responses was then subsequently characterized. Initial studies demonstrated the ability of different vaccine preparations alone or in combinations to induce, in addition to humoral, an S-specific CD4⁺ and CD8⁺ T cell response (Goel et al., 2021; Khoo et al., 2022; Oberhardt et al., 2021; Painter et al., 2021; Payne et al., 2021; Sahin et al., 2021; Stephenson et al., 2021). A comparative analysis of the B and T cell immunogenicity of mRNA, adenovirus-, and protein-based COVID-19 vaccines has been recently published (Zhang et al., 2022b). Similar data for inactivated-virus vaccines are in progress (Lim et al., 2022a).

Of note, the reduced incidence of symptomatic infection observed within 2 weeks after the first dose of mRNA vaccination (Skowronski and Serres, 2021) was not associated with the presence of neutralizing antibodies but rather with the detection of both S-specific T cells and non-neutralizing antibodies that were induced more rapidly after vaccination than neutralizing antibodies (Kalimuddin et al., 2021), demonstrating that vaccine-induced protection was not exclusively mediated by neutralizing antibodies.

It was the progressive emergence of different variants of concerns (VoC) with an increased ability to evade neutralizing antibodies (Cao et al., 2021; Dorp et al., 2021; Liu et al., 2021) that started to shift the previously skewed interest in the immunological correlates of protection from infection (mediated primarily by antibodies) toward correlates of protection from severe disease (mediated by a coordinated presence of humoral and cellular immune response). The high frequency of breakthrough Omicron infection in vaccinated individuals was not associated with a profound loss of efficacy in vaccine-induced protection from severe disease (Collie et al., 2022; Kirsebom et al., 2022). Recent data have also shown that protection from Omicron infection wanes substantially in individuals previously infected with non-Omicron variants (estimation <10% protection after 15 months). However, protection against severe, critical, and fatal COVID-19 due to re-infection remains extremely high (~88%–98%) irrespective of the infecting SARS-CoV-2 variant during primary infection or re-infection (Chemaitelly et al., 2022). These epidemiological observations suggest that T cells play a critical role in the protection from severe disease. SARS-CoV-2-specific T cells wane more slowly than do antibodies (reviewed in Sette and Crotty [2022]), and vaccination and infection induce S-specific T cells that largely, even though not completely, tolerate the amino acid (AA) mutations that characterize the different VoCs, including Omicron (De Marco et al., 2022; Gao et al., 2022; Jung et al., 2022; Keeton et al., 2022; Liu et al., 2022; Naranbhai et al., 2022; Oh et al., 2022; Tarke et al., 2022b).

Therefore, as it has been also recently argued by others (Varadhana et al., 2022), monitoring SARS-CoV-2-specific T cells should be implemented at the population level to better understand which level of T cell response is associated with rapid viral clearance and asymptomatic or pauci-symptomatic control of infection. Admittedly, such a benchmark has been elusive

(Kent et al., 2022) because the reasons for the inability to define a protective T cell threshold are multifaceted.

Firstly, the frequency of detectable SARS-CoV-2-specific T cells in the circulation differs widely, even within a homogeneous cohort of convalescent patients (Dan et al., 2021; Le Bert et al., 2021b). Due to this quantitative heterogeneity, the collection of a vast quantity of data in relation to virological parameters such as the duration or quantity of viral replication is required, but the complexity of testing T cell response makes it hard to execute such a task. Furthermore, cellular immunity induced by vaccination, infection, or by their combination is composed of different populations of T cells specific for different SARS-CoV-2 proteins, with differing functionality and distinct anatomical localization (Figure 1). These variables are likely to significantly affect their antiviral efficacy and should therefore be taken in consideration in defining a measure of protective efficacy involving T cells.

T CELLS AND COVID-19 PATHOGENESIS

Despite the large body of experimental evidence that is establishing associations between the detection of SARS-CoV-2-specific T cells and protection from disease development, concerns have also been raised about the role of T cells in possible pathogenetic damage. Pro-inflammatory, Th1-like immune responses are necessary for viral clearance but can also cause pathology. In severe COVID-19, prolonged and heightened inflammation was associated with global dysregulated activation of both innate and adaptive immunity (Kuri-Cervantes et al., 2020; Laing et al., 2020; Lucas et al., 2020; Mathew et al., 2020). What is the role of T cells in these pathological events? Mild and severe COVID-19 were associated with lymphopenia in blood as well as with an immunophenotype of strong CD4⁺ and CD8⁺ T cell activation (Mathew et al., 2020; Schulien et al., 2021). Activated CD8⁺ T cells were present not only in the circulation but also in pathological lung and brain tissue (Kreutmair et al., 2021; Schwabenland et al., 2021; Szabo et al., 2021; Vijayakumar et al., 2022). However, the antigen specificity of these cells has not been defined, and the T cells detected in locations with observable pathology that show features of T cell activation and exhaustion might merely be bystander immunological events (Lee et al., 2022).

T cells are also not the only component of the immune system that is detected in increased numbers in diseased tissue; increased plasmablast frequency (Kuri-Cervantes et al., 2020) and prolonged type I IFN responses (Zanoni, 2021) were associated with severe COVID-19. Indeed, inflammatory events sustained by myeloid-lineage cells (Domizio et al., 2022), made worse by antibody-mediated uptake of virus (Junqueira et al., 2022), were the more conclusive signals of lung pathogenesis in severe COVID-19 (Kreutmair et al., 2021; Szabo et al., 2021). Of note, when lung and blood samples of patients with severe COVID-19 were analyzed in parallel, higher T cell frequencies in the lung correlated positively with survival, whereas, conversely, higher lung infiltrative myeloid cells correlated with mortality (Szabo et al., 2021). Additionally, prolonged and persistent respiratory symptoms after COVID-19 were associated with an increased presence of composite immune infiltrates in the lung. Imaging showed alterations of the lung parenchyma that

were associated with an increased presence of granulocytes and myeloid cells, whereas increased numbers of B and T cells in the bronchoalveolar lavage (BAL) samples were associated with a range of pulmonary dysfunction. Augmented numbers of CD8⁺ tissue-resident memory (Trm) cells were also associated with signs of persistent ongoing tissue damage (Vijayakumar et al., 2022).

However, more recent work has highlighted the importance of T cell function (and not just quantity and/or presence) in limiting the process of tissue inflammation, shifting attention towards the regular and coordinated sequential modification of CD4⁺ T cells from a mainly Th1 phenotype toward an IFN- γ and IL-10 functional profile (Cardone et al., 2010; Chauss et al., 2021) as a mechanism of viral control without overt pathology. Mouse models of viral respiratory infections have clearly shown the importance of IL-10 production by T cells in shaping their ability to control the virus, while sparing the host from lung pathology (Sun et al., 2009; Zhao et al., 2016a). Of note, asymptomatic SARS-CoV-2-infected patients also demonstrated such a T cell cytokine profile (Le Bert et al., 2021a). In other infection models, the inability of Th1-polarized CD4⁺ T cells to switch towards an IL-10-producing phenotype caused severe tissue damage (Gazzinelli et al., 1996).

The pathogenic role of Th1 cells in SARS-CoV-2 infection was suggested by the findings that T cells present in the bronchoalveolar lavage during ongoing lung inflammation have a classical Th1 cytokine profile (Chauss et al., 2021), and a prolonged Th1 cytokine profile has been demonstrated in patients with severe COVID-19 (Lucas et al., 2020). Importantly, during the recovery from the pathological process of lung inflammation, complement produced by respiratory epithelial cells (Yan et al., 2021) orchestrates a vitamin D-dependent autoregulatory process that resulted in the progressive shutdown of Th1 cytokine production and induction of IL-10 (Chauss et al., 2021). This process appears deficient in severe COVID-19, and, interestingly, the severity of COVID-19 has been associated with vitamin D deficiency in an epidemiological study (Akbar et al., 2021).

It is therefore possible that mechanisms of functional dysregulation in T cells might drive the exacerbated inflammatory events that characterize severe COVID-19 and even some aspects of the prolonged pathology observed in some COVID-19 convalescents (Vijayakumar et al., 2022). Another mechanism of the functional dysregulation of T cells might also involve TGF- β production, which at the moment has been demonstrated to only suppress natural killer (NK) cell function in severe COVID-19 (Witkowski et al., 2021). Changes in the Treg compartment have also been associated with COVID-19 severity (Vick et al., 2021). Nevertheless, as we have summarized, these pathological processes were associated with a quantitative and/or functional deficiency of T cells, whereas no pathological processes have been thus far linked with a robust SARS-CoV-2-specific coordinated CD4⁺ and CD8⁺ T cell response.

DETERMINANTS OF DISEASE PROTECTION: SARS-CoV-2-SPECIFIC T CELL MAGNITUDE, SPECIFICITY, AND IMMUNODOMINANCE

The protective efficacy of antibodies against SARS-CoV-2 infection is restricted to those which are specific to S, because these

antibodies block interaction between the receptor binding domain (RBD) and the ACE2 receptor on host cells, thus preventing the virus from infecting cells. This has become the rationale for current COVID-19 vaccine design as they have successfully reduced the incidence of infection with the ancestral strain of SARS-CoV-2 first detected in Wuhan (Skowronski and Serres, 2021). However, we are now facing SARS-CoV-2 lineages that escape the neutralizing ability of vaccine-induced antibodies (Cao et al., 2021; Liu et al., 2021). It is therefore important to understand whether different SARS-CoV-2 proteins might elicit T cell responses with an increased ability to control viral spread after infection and thus possibly prevent severe disease.

SARS-CoV-2 infection induces CD4⁺ and CD8⁺ T cells specific for different epitopes derived from both structural and non-structural viral proteins (Grifoni et al., 2020; Nelde et al., 2020; Peng et al., 2020; Tan et al., 2021a). Meanwhile, mRNA- and adenoviral-based S vaccines induced only S-specific CD4⁺ and CD8⁺ T cells (Goel et al., 2021; Khoo et al., 2022; Oberhardt et al., 2021; Painter et al., 2021; Stephenson et al., 2021), whereas inactivated-virus vaccines induced CD4⁺ T cells that recognized NPs and S and M proteins (Lim et al., 2022a). A comprehensive summary of all the different SARS-CoV-2 CD8⁺ and CD4⁺ T cell epitopes was presented in a recent review by Kedzierska and Thomas (2022). However, we are still unable to define a clear hierarchy of the SARS-CoV-2 proteins that might generate epitopes triggering CD8⁺ and CD4⁺ T cells with superior protective efficiency (Wellington et al., 2021). Establishing such a hierarchy requires more investigation, bearing in mind that every single viral protein synthesized within an infected cell, including out-of-frame ORFs, and certainly not only S, can generate epitopes presented by histocompatibility leukocyte antigen (HLA) class I that can inform CD8⁺ T cells of the presence of replicating virus. The polymorphism of HLA class I (and HLA class II for CD4⁺ T cells) in human populations implies that the profile of T cell epitopes will be diverse in individuals carrying distinct HLA class I (and class II) molecules that have different abilities to present viral peptides (Nguyen et al., 2020; Saule et al., 2021).

What we can affirm is that the hierarchy of protection linked to an antigen is certainly unrelated, unlike in the case of antibodies, to the architecture of the assembled virion. In other words, CD8⁺ T cells ignore the spatial information that is crucial in determining the utility of an antibody in neutralizing viruses and resolving infection, and instead they are dependent on epitopes derived from structural proteins present within the virus (like NPs) or non-structural proteins involved in viral replication within the infected cells. This paradigm can also be partially applied for CD4⁺ T cells, in the context of intermolecular help. As has been demonstrated in other viral infections (Milich et al., 1987), Tfh cells might recognize hepatitis B virus envelope-specific B cells that display non-envelope epitopes on HLA class II to support their maturation. This could also occur during SARS-CoV-2 infection through the internalization of SARS-CoV-2 virions by B cell receptors (BCRs) that bind S and then present epitopes derived from the structural antigens after antigen processing and association with HLA class II.

Such concepts are supported by experimental data: in non-human primates and mice vaccinated with NP (Harris et al., 2021; Matchett et al., 2021) or envelope and M (Chen et al.,

2022) followed by SARS-CoV-2 challenge, the vaccinated animals exhibited less severe pathology, reduced weight loss, and lower viral loads. This disease protective effect was associated with the rapid recall of antigen-specific T cell responses without robust humoral immune response, demonstrating the protective capacity of T cells specific for different structural proteins of SARS-CoV-2.

Could the abundance of proteins produced during viral replication positively influence protective efficacy through a more robust induction of the cellular immune response? Here, the answer is even more complex, because it is clear that the efficiency of epitope generation affects the quantity of MHC class I and class II peptide complexes assembled and its subsequent ability to activate T cells (Yewdell, 2006), but the quantity of protein produced inside an infected cell is not the sole parameter defining epitope generation (Wu et al., 2019).

In this regard, quantitative analysis of peptides loaded onto MHC class I molecules in SARS-CoV-2-infected cell lines has shown that different viral proteins have differential efficiencies in generating MHC class I restricted epitopes (Weingarten-Gabbay et al., 2021). Proteins produced from non-structural proteins and out-of-frame ORFs of SARS-CoV-2, despite their low quantities in infected cells, generate an abundance of epitopes during early infection (6–12 h). The epitopes derived from out-of-frame proteins (ORF9b) induced a robust virus-specific CD8⁺ T cell response in COVID-19 convalescents, demonstrating their *in vivo* immunogenicity. Conversely, this work reported that the N protein produced very few CD8⁺ T cell epitopes, despite its high protein quantity in infected cells.

The robust immunogenicity of the non-structural proteins of SARS-CoV-2 was also confirmed in other works (Ferretti et al., 2020; Grifoni et al., 2020; Le Bert et al., 2020). In the study of Ferretti et al., for example, *in vitro* analysis of the SARS-CoV-2-specific CD8⁺ T cells toward both structural and non-structural protein epitopes revealed clear multispecificity in CD8⁺ T cells (3–8 epitopes for a single MHC class I), mostly targeting non-S, non-structural proteins. Here, however, the structural N protein was found to be highly immunogenic and generated robust CD8⁺ T cell responses, highlighting how different experimental systems can affect the results as well as the challenges in analyzing CD8⁺ T cell immunodominance in human populations characterized by diverse HLA class I profiles (Nguyen et al., 2020; Saulle et al., 2021).

In any case, a caveat of deriving information about protective efficacy based on the frequency of the T cells is the fact that immunodominance (the hierarchy of proteins based on their induction of CD8⁺ T cell responses) does not necessarily translate into protection. This was demonstrated in a seminal paper on lymphocytic choriomeningitis virus (LCMV) infection (Gallimore et al., 1998). Similarly, this was initially evident in SARS-CoV-2 infection when strong T cell responses against NP and M were first correlated with severity of disease (Peng et al., 2020; Zuo et al., 2021). However, in this specific case, the dominance of T cell responses (likely supported mainly by CD4⁺ T cells) was the consequence of the prolonged production of high quantity of viral antigens present in patients with more severe disease. Subsequently, new data contradicted these findings by showing that M and NP elicit robust responses in asymptomatic patients and that an N-derived T cell immunodominant epitope, like the

one against the HLA-B07/NP105-113 complex, is associated with mild disease (Peng et al., 2021).

If T cell immunodominance could not be taken as a sole parameter of protective efficacy, which other variables should be considered? One variable of likely importance is the kinetic of production of different viral proteins within an infected cell. Coronaviruses have a complex replication strategy that necessitates the initial formation of replication complexes within the cell cytoplasm that support the bulk of viral RNA synthesis (Knoops et al., 2008). Viral replication of RNA viruses within the infected cells does not appear to proceed at a constant rate but rather in well-defined steps with varying production kinetics of each viral protein (Boersma et al., 2020). Theoretically, CD8⁺ T cells capable of recognizing viral proteins produced in the early stage of infection, even before the complete production of virions, might abort viral production. This was, for example, suggested to occur in highly exposed individuals who remained SARS-CoV-2 PCR negative but experienced an innate immune activation and an expansion of NSP-12-specific T cells (Swadling et al., 2021). This possibility is also supported by a recent proteomic analysis performed in cell lines infected with SARS-CoV-2 combined with the characterization of viral peptides presented by HLA class I. Here, it was shown that viral proteins that are expressed early contribute more to HLA I presentation (Weingarten-Gabbay et al., 2021). The authors posited that the robust immunogenicity of NSP-3 protein observed in convalescent individuals (Tarke et al., 2021), despite its low production, might be explained by its early synthesis.

DETERMINANTS OF DISEASE PROTECTION: CROSS-REACTIVE SARS-CoV-2-SPECIFIC T CELLS

SARS-CoV-2 T cell cross-reactivity, namely, the presence of memory T cells induced by previous pathogens (likely by related coronaviruses, but potentially any other pathogens) can also affect immunodominance and the protective efficacy of SARS-CoV-2-specific T cells. Seminal studies in both animal models and humans have demonstrated that T cell cross-reactivity plays a role in the protection from viral diseases but, in selected cases, could also be associated with increased immunopathology (Selin et al., 2004). Several studies conducted within a few months of the onset of the COVID-19 pandemic detected SARS-CoV-2-specific T cells in a significant proportion of individuals (28%–81%) with no previous exposure to SARS-CoV-2 (Braun et al., 2020b; Grifoni et al., 2020; Le Bert et al., 2020; Mateus et al., 2020; Nelde et al., 2020; Sekine et al., 2020; Weiskopf et al., 2020), strongly suggesting that prior exposure to other viruses, likely within the coronavirus family, was able to prime a population of memory SARS-CoV-2-specific T cells. Several studies that tried to define the impact of cross-reactivity on protection from COVID-19 followed, with controversial conclusions (Aran et al., 2020; Gombard et al., 2021; Ringlander et al., 2021). Initial findings suggested that cross-reactive SARS-CoV-2-specific CD4⁺ T cells were rare in patients with COVID-19 and mainly of low affinity (Bacher et al., 2020), arguing against their possible protective role. However, subsequent analysis reported different scenarios. Less severe COVID-19 was detected in individuals with recent exposure to seasonal coronaviruses (Sagar et al., 2020), and the presence of cross-reactive T cells facilitated expansion of

SARS-CoV-2-specific CD8⁺ and CD4⁺ T cell responses during infection (Lineburg et al., 2021; Low et al., 2021) or vaccinations (Loyal et al., 2021; Mateus et al., 2021).

More recent findings add further clinical significance to these observations, showing that a range of cross-reactive T cells of different specificities is actually associated with control of viral replication and abortive infection (Kundu et al., 2022; Swadling et al., 2021) and likely responsible for the rapid T cell response that appears essential for viral control with limited pathology. Among these different cross-reactive T cell specificities, the T cell response against the NSP-12 (RNA-dependent RNA polymerase) protein of SARS-CoV-2 is, in our opinion, of particular interest. Increased frequencies of NSP-12-specific T cells were present in healthy individuals (Swadling et al., 2021; Loyal et al., 2021) and in those who remained PCR and antibody negative despite SARS-CoV-2 exposure. In addition, NSP-12 is highly conserved with a high level of homology between different sarbecoviruses that infect both humans and animals (Swadling et al., 2021). The presence of T cells with such specificity might therefore not only recognize the different emerging lineages of SARS-CoV-2, which to date have mainly accumulated mutations in S, but also could be the basis of a future pan-coronavirus vaccine (Sette and Saphire, 2022).

DETERMINANT OF DISEASE PROTECTION: SARS-CoV-2-SPECIFIC T CELL PROFILE IN HYBRID IMMUNITY

Development of severe disease in vaccinated individuals with SARS-CoV-2 infections is a lower-risk event than in the unvaccinated (Collie et al., 2022; Kirsebom et al., 2022; Tang et al., 2021). However, protection from symptomatic disease induced by infection appears superior to mRNA vaccination alone (Altarawneh et al., 2022). Detailed comparative analyses of viral loads in breakthrough Omicron infection have detected a more rapid control of virus replication in individuals with hybrid immunity (vaccination and infection) in comparison to the individuals vaccinated with three doses of vaccine (Marking et al., 2022). What these studies are suggesting is that vaccination plus infection (Goldberg et al., 2022) provided the host with a superior rapid control of subsequent infection in comparison to vaccination alone.

This is presently a matter of important debate because recent data suggested a reduced ability of Omicron infection to boost a T and B cell response in convalescent individuals who were previously infected with other SARS-CoV-2 variants and then were vaccinated (Reynolds et al., 2022). Even though these data clearly show that previous infection with different SARS-CoV-2 variants can imprint the T and B cell repertoire and suppress the ability of the B and T cells to recognize the variable region of S present in Omicron, this work analyzed immune response only against the mutated region of S (S1) and not against all SARS-CoV-2 proteins. Thus, even though a secondary infection with Omicron might not boost the B and T cells against the mutated region of S, we should not forget that the natural infection in vaccinated individuals can prime a broader SARS-CoV-2-specific T cell response.

The advantages of hybrid immunity over vaccination might not only be a consequence of a broader repertoire of virus-specific an-

tibodies (Reynolds et al., 2021; Stamatatos et al., 2021) and S-specific B cells (Rodda et al., 2022; Terreri et al., 2022) but also be related to the breath of the T cell response (Minervina et al., 2022; Reynolds et al., 2021; Rodda et al., 2022). Individuals with hybrid immunity demonstrated a robust T cell response that was specific not only to S but also to other SARS-CoV-2 proteins with CD4⁺ T cells characterized by a functional profile of IFN- γ and low IL-10 production. This peculiar T cell functional profile has been detected in asymptomatic SARS-CoV-2-infected individuals (Le Bert et al., 2021a), was defective in patients with severe COVID-19 (Chauss et al., 2021), and has been associated with protection from infection without overt lung pathology in mice (Sun et al., 2009; Zhao et al., 2016a). In addition, the recent work by Minervina et al. highlighted that multiple clones of CD8⁺ T cells specific for other SARS-CoV-2 antigens are not reduced in presence by vaccination in individuals first infected and then vaccinated and, perhaps more importantly, in vaccinated individuals who suffered breakthrough infection (Minervina et al., 2022). After infection, non-S virus-specific CD8⁺ T cells expanded robustly upon vaccination, demonstrating that S-based vaccination does not suppress the expansion of T cells specific for other antigens but instead promotes the formation of a broad CD8⁺ T cell repertoire that might better cope with the emergence of novel variants. This study also showed that repeated antigen exposure did not lead to a dysfunction of SARS-CoV-2-specific T cells, despite the expression of T cell exhaustion markers (CTLA-4, PD-1, TIGIT, and Tox) in some SARS-CoV-2-specific CD8⁺ T cells. These CD8⁺ T cells retained their proliferation ability and were cycling, supporting the previous observation that the expression of exhaustion markers in SARS-CoV-2-specific CD8⁺ T cells of COVID-19 convalescent individuals was not associated with functional defects (Rha et al., 2020). Repeated antigen exposure either with vaccination or infection did, however, induce a modification of the memory phenotype, particularly in individuals who were vaccinated after infection. Such modifications were characterized by an increased population of S-specific CD8⁺ effector memory T cells re-expressing CD45RA (TEMRA) that was not observed in individuals who were infected after vaccination (Minervina et al., 2022). The TEMRA S-specific CD8⁺ T cells detected in infected-and-then-vaccinated individuals were characterized by higher granzyme mRNA transcript, a transcriptomic profile observed also in SARS-CoV-2-specific long-lived memory CD8⁺ T cells 6 months/1 year after infection in COVID-19 convalescent patients (Adamo et al., 2022). Whether such differences in T cell phenotype have functional consequences in terms of antiviral efficacy or long term T cell persistence is part of the many unknowns that we need to better characterize.

A further advantage of hybrid immunity is that the antiviral adaptive response is not only localized within the circulatory compartment and/or the lymph node draining the vaccination site (Mudd et al., 2022; Turner et al., 2021). This is discussed in the next section.

DETERMINANT OF DISEASE PROTECTION: SARS-CoV-2-SPECIFIC T CELL LOCALIZATION

The nasal cavity is both the point of entry and the site of initial rapid replication of SARS-CoV-2 (Kuri-Cervantes et al., 2020; Laing et al., 2020; Mathew et al., 2020). Nasal ciliated cells

are readily infected due to their elevated ACE-2 receptor expression and sustain the bulk of initial virus production *in vivo* (Ahn et al., 2021). Infection can then spread to epithelial cells of the lower respiratory tract, particularly in cases of severe COVID-19 (Chua et al., 2020), whereas lower levels of viral replication can occur in other extra pulmonary sites, e.g., liver, kidney, heart, brain, and gut (Braun et al., 2020a; Puelles et al., 2020; Wanner et al., 2022). In contrast, blood cells are not the primary site of SARS-CoV-2 infection and, except in cases of severe COVID-19, SARS-CoV-2 was rarely detectable in the circulation (Andersson et al., 2020). Nevertheless, most of our analysis of the cellular (but also humoral) immune response has been confined to the circulatory compartment. This should be a cause of concern because seminal work in mice infected with coronaviruses (Middle East respiratory syndrome coronavirus as well as SARS-CoV) demonstrated the importance of the presence of coronavirus-specific memory CD4⁺ T cells in the airway. In this model, protection from disease was mediated by the ability of CD4⁺ T cells resident in the upper airway to secrete IFN- γ and recruit virus-specific CD8⁺ T cells (Zhao et al., 2016b).

Tissue-resident virus-specific CD8⁺ T cells can also act as a first layer of protection and activate innate and adaptive immunity mechanisms that achieve rapid “near sterilizing immunity” (Schenkel et al., 2014). In infection with other respiratory viruses, such as influenza or respiratory syncytial virus, the presence or the adoptive transfer of tissue-resident CD8⁺ T cells into the nasal cavity controlled viral spread and disease severity (Kinneer et al., 2018; Pizzolla et al., 2017a). Lung-resident virus-specific T cells producing IL-10 have also been associated with viral clearance with limited pathology (Sun et al., 2009). Finally, the protective value of the specific induction of SARS-CoV-2-specific cellular immunity in the upper airway was recently supported by works of different groups in SARS-CoV-2-vaccinated infected mice (Afkhami et al., 2022; Ishii et al., 2022; Mao et al., 2022) and hamsters (Langel et al., 2022). In some of these models, the importance of eliciting a mucosal-specific antibody protection should not be discounted (Afkhami et al., 2022; Langel et al., 2022; Mao et al., 2022), but in others, the major contribution of vaccine-induced mucosal T cells in protection was clear (Ishii et al., 2022).

In humans, acute SARS-CoV-2 infection causes a dynamic modification of immune cell populations in different tissues (nasal, oropharyngeal cavity, as well as in the lung): a preferential recruitment of granulocytes, inflammatory monocytes, macrophages, and NK cells was observed (Roukens et al., 2022). However, T cell enrichment was also present and likely caused by elevated levels of chemokines secreted in the tissues, which have been shown to be proportional to SARS-CoV-2 replication (Cheemarla et al., 2021).

After SARS-CoV-2 resolution, tissue-resident SARS-CoV-2-specific memory T cells were found in bone marrow, spleen, lung, and lymph nodes (Poon et al., 2021). These SARS-CoV-2-specific T cells persisted at least 6 months after infection, and their detected frequency correlated with that of circulating T cells. Tissue-resident S-specific CD8⁺ T cells were also observed in the nasal cavity after resolution of acute SARS-CoV-2 infection (Roukens et al., 2022). SARS-CoV-2-specific T cells can also be detected in the oropharyngeal tonsils and

in BAL specimens of healthy individuals who never had contact with SARS-CoV-2 (Maini et al., 2022; Niessl et al., 2021b). They expressed classical tissue-resident phenotype markers (CD103⁺ and CD69⁺) and the follicular homing marker CXCR5. In addition, they were polyfunctional, producing Th1 cytokines with a preferential production of TNF- α and low IFN- γ . Tonsil-resident SARS-CoV-2-specific T cells also displayed, in adults but not in children, a lower capacity to secrete Th1 cytokines than CD8⁺ T cells specific for other viruses like Epstein-Barr virus, human cytomegalovirus, and seasonal coronavirus (Niessl et al., 2021b). Because these SARS-CoV-2-specific T cells were likely induced by infection with other seasonal coronaviruses, this partial functionality might be caused by their lower affinity to the SARS-CoV-2 peptides used for stimulation. Whether these tissue-resident cross-reactive T cells have a protective effect is therefore still debatable. Nevertheless, these tissue-resident T cells were shown to recognize multiple SARS-CoV-2 epitopes present in structural and non-structural proteins.

Of note, increasing experimental evidence suggests that SARS-CoV-2-specific T cells in the lung and oropharyngeal cavity are differentially regulated than the ones present in the nasal cavity. Animal models of viral respiratory infections demonstrated that nasal-associated lymphoid tissues were not the site of induction of virus-specific T cells, but do they recruit and support the persistence of tissue-resident T cells specific for respiratory viruses primed initially in the more organized lymphoid organs present in the oral cavity (oropharyngeal and palatin lymph nodes) (Pizzolla et al., 2017a, 2017b).

An open question is whether the parenteral COVID-19 vaccines increased the frequency of tissue-resident T cells in the primary airway. A study reported very high frequencies (up to 20% of total T cells) of S-specific T cells in the nasal cavity of individuals vaccinated with mRNA vaccines (Ssemaganda et al., 2022). Such data were, however, at odds with the apparent exclusive localization of tissue-resident S-specific T cells in the lymph node draining the site of mRNA injections (Lederer et al., 2022; Mudd et al., 2022; Turner et al., 2021) and also with recent works that detected tissue-resident S-specific T cells only in the nasal cavity or BALB of vaccinated individuals who experienced a breakthrough infection but not in those of healthy COVID-19 vaccinees (Lim et al., 2022b; Tang et al., 2022). Of note, in these vaccinated individuals with breakthrough infection, nasal-resident SARS-CoV-2-specific CD4⁺ and CD8⁺ T cells produced high quantities of IFN- γ . They were also able to recognize different epitopes located in different non-S proteins (Lim et al., 2022b), similar to what was detected in the circulatory compartment (Minervina et al., 2022), supporting the idea that vaccination does not suppress the induction of a broader SARS-CoV-2-specific T cell repertoire at the site of initial infection.

If confirmed by other studies, the requirement of natural infection to induce a robust SARS-CoV-2-specific T cell immunity in the nasal cavity might have important consequences. Nasal-resident memory T cells can represent one important feature of individuals with hybrid immunity, which might be capable of rapidly curtailing SARS-CoV-2 replication with consequences not only for the infected host but also for viral shedding into the community.

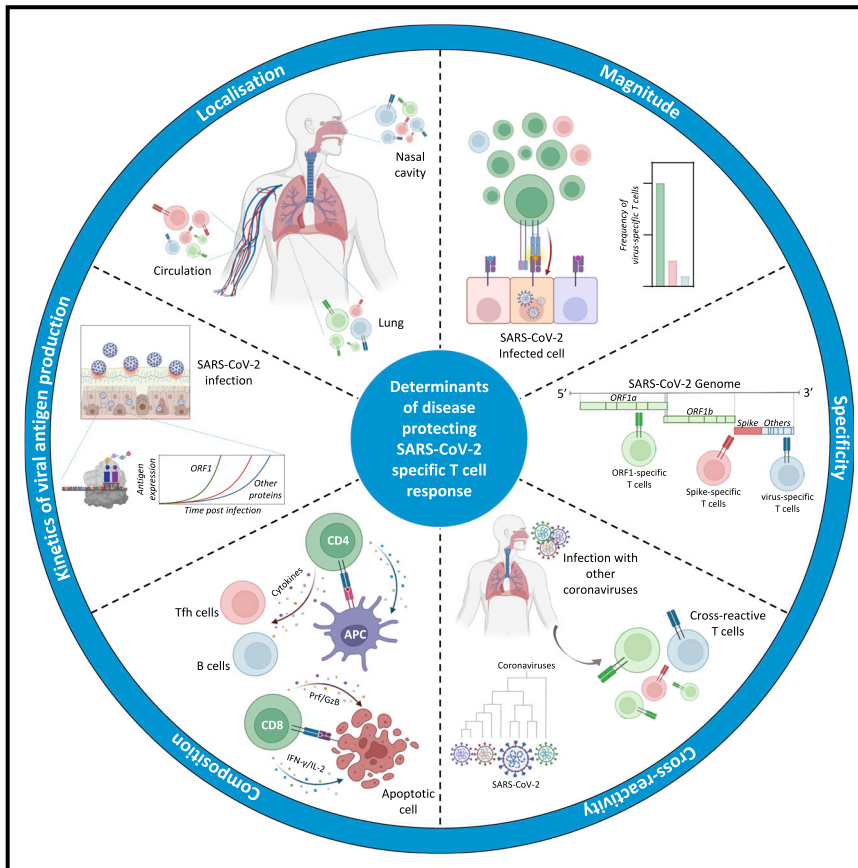


Figure 2. The determinants of disease-protecting SARS-CoV-2-specific T cell responses

This illustration summarizes the six proposed determinants of antigen-specific T cell responses that can mediate protection against COVID-19 disease. Magnitude refers to the quantitative measurement of sampled total SARS-CoV-2-specific T cells derived from flow cytometry or ELISpot assays. Specificity refers to the T cell recognition of various structural or non-structural protein targets, particularly their derived epitopes, that are presented by MHC molecules. Of consequent interest are the antigenic breadth and associated hierarchies of disease protection or immunodominance. Cross-reactivity refers to the ability of a T cell, primed by other antigens, to recognize MHC-presented SARS-CoV-2-derived epitopes. Antigenic history, likely to related coronaviruses, could shape an individual's protective responses to SARS-CoV-2 encounter. Composition refers to the T cell subsets (i.e., CD4⁺ and CD8⁺) and their associated niches and cytokines produced during antigen encounter or infection. Kinetics of viral antigen production is a virological property referring to the succession of translation of SARS-CoV-2 mRNA during infection, which could influence T cell-mediated protection against disease. Localisation refers to the anatomic niche(s) occupied by protective SARS-CoV-2-specific T cells.

of SARS-CoV-2 infection. The initial claim that the T cell response against SARS-CoV-2 was mainly supported by CD4⁺ T cells has since been revised as it became clear that CD8⁺ T cells were robustly induced early after infection

CONCLUDING REMARKS: CD4⁺ VERSUS CD8⁺ AND VIRAL ABILITY TO ESCAPE T CELLS

The virological landscape of the COVID-19 pandemic was radically modified by the emergence of new SARS-CoV-2 lineages that were able to escape the neutralizing ability of antibodies elicited by vaccines based on the S protein of the ancestor Wuhan isolates (Collie et al., 2022). Like others (Vardhana et al., 2022), we believe that such changes necessitate a more comprehensive analysis of vaccine immunogenicity that should not be based solely on antibody assessments but also require a comprehensive evaluation of virus-specific cellular immunity. However, because we also believe that the evaluation of the protective efficacy (against severe disease) of SARS-CoV-2-specific T cells cannot be based only on quantitative measurements, we reviewed the variables that can impact the protective efficacy of T cells (Figure 2).

Certainly, our summary is not exhaustive. Leaving aside some hypotheses that have surfaced recently—for example, the ability of the SARS-CoV-2 S protein to directly activate T cells with a super-antigen like mechanism (supported at the moment only by in silico models of conformational identity between part of S with Staphylococcus enterotoxin B; Cheng et al., 2020)—other important variables remain to be properly elucidated. We still do not have complete answers to simple questions, like the differential impact of CD4⁺ or CD8⁺ T cells in the immunopathogenesis

(Ferretti et al., 2020; Schuijen et al., 2021), and the quantitative differences detected in convalescent individuals (Bonifacius et al., 2021; Breton et al., 2021; Dan et al., 2021; Grifoni et al., 2020; Le Bert et al., 2020; Rodda et al., 2021; Weiskopf et al., 2020) were due to differential kinetics of expansion and contraction of the two populations (Bertoletti et al., 2021b). Nevertheless, the impact that SARS-CoV-2-specific CD8⁺ or CD4⁺ T cells exert in the protection from disease development remains uncertain.

Protection mediated by vaccines that do not trigger the production of neutralizing antibodies is dependent on the function of CD8⁺ T cells (Ishii et al., 2022; McMahan et al., 2021). Furthermore, presence of CD8⁺ T cells is associated with early recovery of COVID-19 in patients with hematological cancers and humoral defects (Bange et al., 2021). At the same time, as we quoted previously, the induction of CD4⁺ T cells specific for the NP of SARS-CoV in the nasal cavity of mice protected the animals from lethal disease after infection with different coronaviruses (Zhao et al., 2016a), and a robust CD4⁺ T cell response seems required in individuals with co-morbidities (i.e., cancers) to reduce long-term SARS-CoV-2 infection (Lyudovyyk et al., 2022). Furthermore, some clinical observations in individuals infected with HIV have suggested that helper CD4⁺ T cells might play an important role in reducing the establishment of prolonged infection and protecting from severe COVID-19. Prolonged shedding of high quantities of SARS-CoV-2 has been observed in HIV-positive individuals (particularly the ones with

low CD4⁺ counts) (Meiring et al., 2022), and HIV positivity has been shown to be an independent risk factor for hospital admission and mortality (Bertagnolio et al., 2022).

We think that studies that compare the protective efficacy against disease development induced by vaccination with mRNA- and inactivated-virus-based vaccines might help to provide additional clarity on the role played by virus-specific CD8⁺ and CD4⁺ T cells in SARS-CoV-2 infection. Inactivated-virus vaccines, differently than S mRNA-based vaccines, induce a T cell response that recognizes multiple different proteins but is mediated exclusively by CD4⁺ T cells (Lim et al., 2022a). The recently reported apparent efficacy of inactivated-virus-based vaccines in reducing disease severity in the recent Omicron infection wave in Hong Kong (McMenamin et al., 2022) suggests that the breadth of a vaccine-induced multi-protein-specific CD4⁺ T cell response might compensate for the absence of CD8⁺ T cell responses in controlling Omicron-induced pathology.

Another aspect of SARS-CoV-2-specific T cell immunity that has, thus far, been not sufficiently studied is not related to the quantity, function, or localization of T cells but rather on the ability of SARS-CoV-2 to escape them. The mutations accumulated by the different SARS-CoV-2 lineages within S and other proteins do not fully escape the recognition of the broad repertoire of T cells induced by infection or by vaccination. However, this does not mean that some mutations could not abolish T cell recognition of selected epitopes (Agerer et al., 2021; De Silva et al., 2021; Dolton et al., 2022; Motozono et al., 2021) and that these mutations might not, in selected individuals, induce a substantial reduction of T cell recognition. This has been observed mainly for CD8⁺ T cell epitopes (Dolton et al., 2022; Naranbhai et al., 2022), but evidence of reduced S-specific CD4⁺ T cell activation has also been reported (Reynolds et al., 2022). Furthermore, research has only just started to analyze the impact that AA mutations located not within the T cell epitopes but in flanking regions might have in SARS-CoV-2 T cell epitope generation (Wellington et al., 2022).

However, viruses might not only accumulate mutations that allow escape from T cell recognition but also have intrinsic ability to alter the pathway leading to antigen processing and presentation of HLA class I epitopes (Pishesha et al., 2022).

Many viruses possess strategies that are evolutionarily maintained to allow the virus to survive in the face of a robust CD8⁺ T cell response (Lorenzo et al., 2001). Evidence in the literature has started to show that SARS-CoV-2 can affect both processing and presentation. A significant reduction of proteins involved in the ubiquitination pathway and of POMP, a chaperone protein critical for the assembly of 20S proteasome and immunoproteasome, was detected in different SARS-CoV-2-infected cell lines (Weingarten-Gabbay et al., 2021), suggesting that SARS-CoV-2 infection could reduce processing of newly produced viral proteins. Finally, a reduction of HLA class I molecule expression after SARS-CoV-2 infection of different cell lines has been reported. Initial data suggested that two proteins, ORF-6 and ORF-8, were responsible for this phenomenon: ORF-6 by suppressing the transcriptional upregulation of HLA class I (Yoo et al., 2021), and ORF-8 might act post-transcriptionally by directing an HLA-A201 molecule towards an autophagosome degradation pathway (Zhang et al., 2021b). More recent data

have focused the attention to two other accessory proteins, ORF3a and ORF7a (Arshad et al., 2022; Zhang et al., 2022a). ORF3a acts as a pore-forming viral protein that alters host protein trafficking and ionic homeostasis (Kern et al., 2021). Like other viruses that also produce such pore-forming proteins, ORF-3a downregulates HLA class I expression. ORF7a, however, appears to downregulate MHC class I expression by competing directly with beta-2-microglobulin for binding with the MHC class I heavy chain (Arshad et al., 2022). However, the real overall impact of all these mechanisms on the ability of SARS-CoV-2 to evade CD8⁺ T cell recognition has not been yet directly evaluated. *In vitro* analysis showed a reduction of 20%–30% of HLA class I expression, and the functional consequences of such reduction will have to be further elucidated.

Overall, the SARS-CoV-2-specific T cell response will require continued evaluation in order to clearly define its role in controlling an infection and its associated disease by a virus that has shown great ability to escape humoral response.

More data on T cell responses in large clinical trials of vaccine protection in different populations might be facilitated by recently developed new methods that can provide a rapid estimation of the quantity, diversity, and function of SARS-CoV-2-specific T cells in samples (Dalai et al., 2022; Murugesan et al., 2020; Pogorely et al., 2022; Schwarz et al., 2022; Tan et al., 2021b). Animal models that are better at recapitulating human SARS-CoV-2 infection (Fumagalli et al., 2022; Zhuang et al., 2022) will also be employed to define the mechanism of the protective T cell response. Finally, studies that evaluate the ability of human T cells to recognize virus-infected cells, and not only peptide-pulsed cells, are urgently needed to complete the functional portrait of this critical component of our immune system.

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DECLARATION OF INTERESTS

A. Bertoletti, N. Le Bert and A.T. Tan reported a patent for a method to monitor SARS-CoV-2-specific T cells in biological samples pending and are the co-founders of T Cell Diagnostic (TCD), Ltd.

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