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REVIEW

T cell responses to SARS-CoV-2 in humans and animals

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SARS-CoV-2, the causative agent of COVID-19, first emerged in 2019. Antibody responses against SARS-CoV-2 have been given a lot of attention. However, the armamentarium of humoral and T cells may have differing roles in different viral infections. Though the exact role of T cells in COVID-19 remains to be elucidated, prior experience with human coronavirus has revealed an essential role of T cells in the outcomes of viral infections. Moreover, an increasing body of evidence suggests that T cells might be effective against SARS-CoV-2. This review summarizes the role of T cells in mouse CoV, human pathogenic respiratory CoV in general and SARS-CoV-2 in specific.

Keywords: SARS-CoV-2, T cell, coronavirus, immune response

Introduction

Coronaviridae, a family of enveloped single-stranded RNA viruses, consists of two sub-families Orthocoronavirinae and Letovirinae (Pillaiyar *et al.*, 2021; Zhou *et al.*, 2021). Orthocoronavirinae is divided into four genera: Alpha, Beta, Gamma, and Deltacoronavirus. Betacoronavirus includes mouse corona virus (mouse-CoV or mouse hepatitis virus, MHV), severe acute respiratory syndrome coronavirus corona virus 1 (SARS-CoV-1), Middle East respiratory syndrome-CoV (MERS-CoV) and SARS-CoV-2. Mouse-CoV has been adopted as a model to study human CoV (Körner *et al.*, 2020). The infection with the human CoV is commonly associated with mild respiratory symptoms. However, the emergence of beta subgroup CoV strains, including SARS-CoV-1, MERS-CoV, and SARS-CoV-2, highlights the potential of CoV to cause severe respiratory and systemic disease (Van Der Hoek *et al.*, 2004; Sariol and Perlman, 2020; Grabherr *et al.*, 2021).

SARS-CoV-1-infected individuals were first reported in 2002 with approximately 8100 reported cases (Peng *et al.*, 2003; Zhao *et al.*, 2003; Sariol and Perlman, 2020). MERS-CoV was identified in 2012 with approximately 2,500 confirmed cases (Zaki *et al.*, 2012). Recently on December 31, 2019, pneumonia caused by an unknown cause was stated to world health organization (WHO), which was later called Coronavirus disease 2019 (COVID-19), of which causative agent is SARS-CoV-2 (Zhou *et al.*, 2020), a highly contagious novel CoV (Hartley *et al.*, 2020). In January 2020, World Health Organization declared COVID-19 an international public health emergency. As of November 29, 2021, more than 260 million people have been infected and more than 5.0 million deaths have been reported worldwide (WHO, 2021). All these three strains, including SARS-CoV-1, MERS-CoV, and SARS-CoV-2, can cause severe pneumonia (Cleri *et al.*, 2010; Naeem, 2013; Wang *et al.*, 2020; Yang *et al.*, 2020). However, SARS-CoV-1 and MERS-CoV have limited person-to-person transmission, eventually resulting in a lower number of confirmed cases (Sariol and Perlman, 2020), compared with SARS-CoV-2.

Antibody responses induced in patients previously infected with influenza A virus or SARS-CoV-1 tends to be short-lived (Tang *et al.*, 2011). In contrast, memory T cells can be detected even after 6 years of infection in SARS-CoV-1 recovered patients. An understanding of SARS-CoV-2-specific T cell responses and more importantly how this particular arm of immune system can be improved to develop more efficient vaccines is the need of the hour.

This review provides a brief summary of roles of $CD4^+$ and $CD8^+$ T cells in mouse-CoV, MERS-CoV and SARS-CoV-1, and then explores roles of different T cells in SARS-CoV-2 in animal models and humans.

Role of $CD4^+$ and $CD8^+$ T Cells in Mouse-CoV

Mouse-CoV, a group of highly related viral strains, cause a variety of diseases in mice, including enteric disease, hepatitis, respiratory disease, encephalitis, and chronic demyelination depending on viral strain, route of infection, age, immune status, and genetic background of the mice (Weiss and Navas-Martin, 2005; Körner *et al.*, 2020). As such, some mouse-CoVs have been adopted as a model to study human CoV (Körner *et al.*, 2020). For example, MHV-A59 induces acute pneumonia and severe lung injuries in young and old C57BL/6 mice, closely resembling acute respiratory distress syndrome (ARDS) caused by MERS-CoV and SARS-CoV-1.

Both $CD8^+$ and $CD4^+$ T cells were shown to be required for the clearance of mouse-CoV (MHV-JHM; MHV-4) (Williamson and Stohlman, 1990; Yamaguchi *et al.*, 1991). C57BL/6

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mice, resistant to mouse-CoV, possess dominant mouse-CoV (MHV-1) specific CD8$^+$ T cells both in the breadth and magnitude (Khanolkar *et al.*, 2010), predicting the protective role of CD8$^+$ T cells. Moreover, in CD8$^+$ T cell-depleted mice, antibody response plays a minimal role in controlling the infection (Williamson and Stohlman, 1990). CD8$^+$ T cells expressing CCR7 sense the expression of CCR7 ligands at the site of inflammation (central nervous system) induced by challenging C57BL/6 intranasally with mouse-CoV (MHV A59) (Cupovic *et al.*, 2016). Moreover, polyfunctional CD8$^+$ T cells were demonstrated to be critical for the successful elimination of the virus. On the other hand, CD4$^+$ T cells provide crucial helper functions in optimizing activation and antiviral properties of CD8$^+$ T cells (Phares *et al.*, 2012) and resistance to mouse-CoV (MHV-3) requires Th1 development (Liu *et al.*, 1998). However, in some strains of mouse-CoV, elevated immune response can be deleterious. For example, in contrast to MHV-A59 and MHV-JHM, MHV-1 induced severe lung damage, which correlated better to the elevated inflammatory immune responses than to viral replication in the lung, predicting that the damage is mainly immunopathological (Leibowitz *et al.*, 2010).

Role of CD4$^+$ and CD8$^+$ T cells in SARS-CoV-1 and MERS-CoV

Protective role of T cells against SARS-CoV-1 has been analyzed (Zhao *et al.*, 2010; Channappanavar *et al.*, 2014). CD4$^+$ T cell-depleted BALB/c mice show delayed clearance of SARS-CoV-1 from the lungs (Chen *et al.*, 2010). Although SARS-CoV-1-specific CD4$^+$ T cells and antibody responses were necessary for complete protection, CD8$^+$ T cell response was critical to protect C57BL/6 mice from lethal SARS-CoV-1 (MA15, mouse-adapted strain) infection (Channappanavar *et al.*, 2014).

Adoptive transfer of serum from vaccinated (Venezuelan equine encephalitis replicon particles expressing MERS-CoV spike [S]-protein, VRP-S) BALB/c mice to naive mice 1-day before challenge significantly reduced the viral load as early as 1-day post-challenge (DPC) (Zhao *et al.*, 2014). However, in contrast to B cell knockout (μMT), T cell knockout (TCRα-/-KO) or SCID BALB/c mice did not clear MERS-CoV, suggesting a more important role played by T cells in the protection against viral infection.

SARS-CoV-1-specific T cell responses have been analyzed in peripheral blood mononuclear cells (PBMCs) of human convalescents by using overlapping peptides covering the whole proteome of the virus (Li *et al.*, 2008). These specific T cells were shown to be essential for the clearance of infected cells, especially in the lungs (Gu *et al.*, 2005). In contrast to waning antibody and memory B cell responses, durable and long-lived memory T cell responses has been detected in recovered patients (Chen *et al.*, 2005; Peng *et al.*, 2006; Yang *et al.*, 2006, 2007; Fan *et al.*, 2009; Oh *et al.*, 2011; Tang *et al.*, 2011; Da Guan *et al.*, 2015; Ng *et al.*, 2016). A strong MERS-CoV S-protein-specific T cell response was described in a patient on the 24th-day post symptom onset (PSO) (Da Guan *et al.*, 2015). Th1-associated cytokines (IL-2 and IFN-γ) have been reported to decrease in a fatal case compared to a patient who survived the infection (Faure *et al.*, 2014), implying the importance of the development of effective T cell responses in combating the disease.

Role of CD4$^+$ and CD8$^+$ T Cells in SARS-CoV-2

T cell epitopes

Parts of antigens that are specifically recognized by lymphocytes are called determinants or epitopes. HLA class I and HLA class II restricted epitopes are generally 8 or 11 and 13–17 residues long, respectively, although longer and shorter epitopes have also been defined. In the context of SARS-CoV-2, a variety of screening methodologies have been used to identify specific epitopes, including varying size of epitopes, evaluation of responses either directly *ex vivo* or after an *in vitro* culture re-stimulation, and various readout types (ELISA, ELISpot, AIM, ICS, tetramer staining, or mass spectrometry) (Grifoni *et al.*, 2021; Pan *et al.*, 2021). A detailed

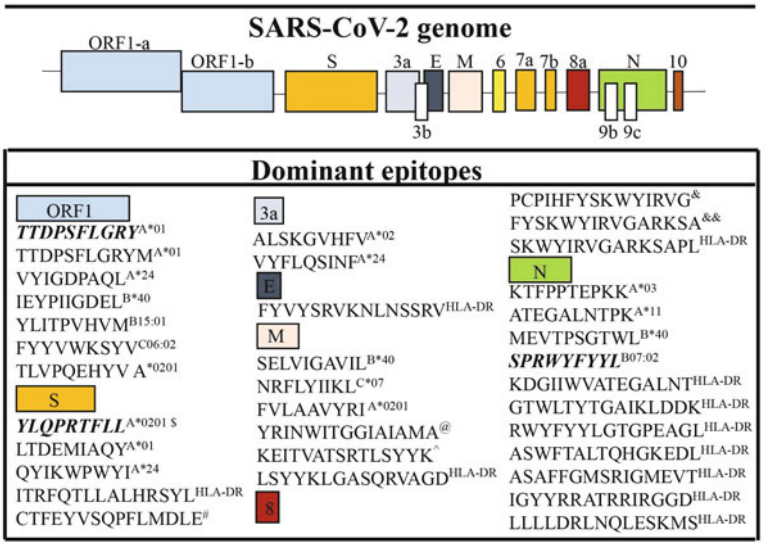


Fig. 1. SARS-CoV-2 specific CD4$^+$ and CD8$^+$ T cell immunodominant epitopes in humans. The dominant epitopes (≥ 50% individuals responded to a specific epitope in a particular study, and at least 3 individuals responded) were summarized from multiple studies (Keller *et al.*, 2020; Shomuradova *et al.*, 2020; Nelde *et al.*, 2021; Nielsen *et al.*, 2021; Saini *et al.*, 2021; Tarke *et al.*, 2021). Text in italics and bold represents frequently reported immunodominant epitopes in the literature. $, same epitope showed 33.04% detection in multimer staining. #, @, ^, &, && represent different restricting HLA molecules: #, DQB1*02:01, DQB1*02:02, DQB1*05:02, DQB1*05:03, DRB1*07:01, DRB1*16:01; @, DQB1*02:02, DQB1*03:01, DQB1*05:01, DQB1*05:02, DQB1*05:03, DQB1*06:02, DQB1*06:03, DRB1*07:01, DRB1*10:01, DRB1*12:01, DRB1*13:01, DRB1*14:01, DRB1*15:01, DRB1*16:01; ^, DQB1*06:03, DRB1*03:01, DRB1*07:01, DRB1*14:01, DRB1*14:06, DRB1*15:01, DRB1*16:02; &, DRB1*08:02, DRB1*13:01, DRB1*15:01, DRB1*15:02, DRB1*16:01; &&, DQB1*06:01, DRB1*04:02, DRB1*07:01, DRB1*11:01, DRB1*11:04, DRB1*13:03, DRB1*14:01, DRB1*14:06, DRB1*15:01, DRB1*15:02, DRB1*16:01, DRB1*16:02.

review of SARS-CoV-2 human T cell epitopes has been done (Grifoni *et al.*, 2021). Numerous peptides have been reported to be immunodominant in several studies mainly because each study used different subjective criteria of immunodominance. For example, epitopes frequently targeted by T cells in 6 or more of the 34 participants (Peng *et al.*, 2020), 3 of 13 participants (Grifoni *et al.*, 2021), immune responses induced in ≥ 50% of tested (Nelde *et al.*, 2021; Saini *et al.*, 2021) and so on. Of note, 3 peptides (open reading frame ORF1; TTDPSFLGRY, S; YLQPRTFLL, nucleocapsid N; SPRWYFYYL) have been reportedly confirmed to be immunodominant in various studies (Grifoni *et al.*, 2021; Wellington *et al.*, 2021). Herein, we briefly summarize the dominant epitopes in SARS-CoV-2 as per the following definition (Nelde *et al.*, 2021; Saini *et al.*, 2021): T cell reactivity to an epitope in ≥ 50% clinical samples (Fig. 1).

In infected individuals, $CD4^+$ T cells have been shown to recognize a range of SARS-CoV-2 antigens (Braun *et al.*, 2020; Grifoni *et al.*, 2020; Le Bert *et al.*, 2020; Lucas *et al.*, 2020; Peng *et al.*, 2020; Thieme *et al.*, 2020; Nelde *et al.*, 2021; Sette and Crotty, 2021). Overall, S, M, and N proteins contain higher numbers of $CD4^+$ T cell epitopes than other viral proteins when assayed on PBMCs from SARS-CoV-2-infected subjects (Grifoni *et al.*, 2020) (Fig. 1A). It is also worthy to note that the response was also directed against other viral proteins as well: nonstructural protein (Nsp)3, Nsp4, ORF3a, ORF8, ORF7a, and Nsp12. Similarly, $CD8^+$ T cells are specific for a range of SARS-CoV-2 antigens (Braun *et al.*, 2020; Gangaev *et al.*, 2020; Grifoni *et al.*, 2020, 2021; Le Bert *et al.*, 2020; Peng *et al.*, 2020; Nelde *et al.*, 2021; Saini *et al.*, 2021) (Fig. 1). In addition, polyfunctional $CD8^+$ T cell responses directed against membrane/nucleocapsid (M/N)-proteins were broader than S protein (Peng *et al.*, 2020). Recently, Pan *et al.* (2021) identified $CD8^+$ T cell epitopes in Nsp13 by using mass spectrometry. Of note, Nsp13 peptide-specific CTLs observed in the peripheral blood were able to recognize and lyse SARS-CoV-2-infected target cells. Although this study was not extensive, the identified epitopes are highly conserved, immunogenic, and presented by highly prevalent allelotypes. Furthermore, additional epitopes to these and other nonstructural proteins need to be sought, broadening the panel for T cell-based responses which would facilitate the development of effective subunit vaccines and T cell therapy in the future (Pan *et al.*, 2021).

The pattern of SARS-CoV-2 antigens recognized (evaluated by IFN-γ ELISpot) appears to be similar (non-significant difference) during acute, convalescent, and memory phases (Rydyznski Moderbacher *et al.*, 2020). However, interestingly ORF7/8 specific cells may be more selective for acute phase than convalescent phase (Tan *et al.*, 2021). The increased immunogenicity of ORF7/8 during early active phase of infection might be investigated further as the mechanism is not clearly understood, which can be due to accelerated selective expansion, preexisting immunity or some other reasons.

T cells in mice and non-human primates

Presently different animal models are used to evaluate immune responses and pathogenicity of SARS-CoV-2, including mice expressing human angiotensin I-converting enzyme 2 (hACE2) (Muñoz-Fontela *et al.*, 2020) and mice expressing mRNA-induced hACE2 receptor. Upon infection, hACE2 expressing mice showed $CD4^+IFN\text{-}\gamma^+$ and $CD8^+IFN\text{-}\gamma^+$ cells in the blood during a prime-boost infection (Hassert *et al.*, 2020). Mice vaccinated with VRPs expressing four structural proteins (S, N, M, or E), six accessory proteins (ORF3a, ORF6, ORF7a, ORF8, ORF9b, or ORF9c) or various T cell epitopes, showed that SARS-CoV-2-specific T cells ($CD4^+$ and $CD8^+$ T cells) were polyfunctional and were able to lyse peptide-loaded target cells *in vitro* (Zhuang *et al.*, 2021). In bronchoalveolar lavage (BAL) dominant $CD4^+$ T cell epitopes were found in N protein and ORF3a in BALB/c (N351-365, ILLNKHIDAYKTFPP) and C57BL/6 mice (ORF3a266-280, EPIYDEPTTTTSVPL), respectively (Zhuang *et al.*, 2021). In contrast, dominant $CD8^+$ T cell epitopes were identified in S-protein in both BALB/c (S535-543, KNKCVNFNF) and C57BL/6 (S538-546, CVNFNFNGL) mice. In addition, VRPs expressing only immunodominant T cell epitopes partially protected the mice in the absence of neutralizing antibodies, hinting on the protective roles of T cells. For example, $IFN\text{-}\gamma^+CD4^+/CD8^+$ T cells induced by VRP-N351-365 or VRP-S-538-546 vaccination partially protected mice from severe disease and these cells peaked at 8-10 DPC in airway, lung tissue, draining lymph nodes (DLNs) and spleens. On the other hand, in rhesus macaques, $CD4^+$ central memory T cells were significantly induced at 5 days post re-challenge (DPR) in lymph nodes compared with 5 days post-infection (5 DPI) (Deng *et al.*, 2020). Moreover, activated $CD8^+$ T cells were significantly increased in blood at 14 DPI and 28 DPI compared to 0 DPI, when they were re-challenged. On re-challenging *Macaques mulatta*, which have been depleted of $CD8^+$ T cells after primary challenge, displayed breakthrough virus shedding in nasal swabs irrespective of CD8α or CD8β depletion. These data demonstrate virus-specific T cells responses play a protective role against the virus (McMahan *et al.*, 2021).

Role of $CD4^+$ and $CD8^+$ T cells in humans

SARS-CoV-2-specific $CD4^+$ T cells have been shown to differentiate into Th1 and Tfh T cells (Grifoni *et al.*, 2020; Neidleman *et al.*, 2020; Weiskopf *et al.*, 2020). Th1 have antiviral properties and Tfh are specialized in providing help to B cells and thus are pivotal for the development of neutralizing antibodies and memory B cells. While Th2 cells are associated with lung immunopathology in SARS-CoV-1 infection (Deming *et al.*, 2006; Yasui *et al.*, 2008), the dominant cytokine produced by SARS-CoV-2-specific $CD4^+$ T cells was IFN-γ followed by TNF and IL-2 which is a signature of canonical Th1 cell activation (Grifoni *et al.*, 2020; Weiskopf *et al.*, 2020). It was further demonstrated that virus-specific $CD4^+$ and $CD8^+$ T cells were detectable in approximately 100% and 70–80% of convalescents (Grifoni *et al.*, 2020; Weiskopf *et al.*, 2020). A similar trend in $CD4^+$ and $CD8^+$ T cells has been seen in acute cases. For example, a study of 10 COVID-19 patients with moderate to severe ARDS, requiring invasive mechanical ventilation, SARS-CoV-2 S-protein-specific $CD4^+$ and $CD8^+$ T cells were detected in 10 and 8 patients, respectively (Weiskopf *et al.*, 2020). $CD4^+$ T cell responses were predominantly Th1 type, however, relatively lower Th2 and Th17 cytokines were also detected. In contrast, Grifoni *et*

al. (2020) reported negligible Th2- or Th17-related cytokines in convalescents. In consistent with notion, a study (n = 9), which detected SARS-CoV-2-specific T cells with CyTOF, demonstrated that S-specific peripheral Th2 and Th17 cells were not detected in convalescents from mild disease (Neidleman *et al.*, 2020). SARS-CoV-2-specific $CD8^+$ T cells possess high levels of effector molecules, including IFN-γ, granzyme B, perforin, and CD107a (Rydyznski Moderbacher *et al.*, 2020; Sekine *et al.*, 2020; Schulien *et al.*, 2021). Early after the emergence of COVID-19, several studies reported an exhausted phenotype, including programmed cell death protein-1 (PD-1) expressing $CD8^+$ T cells in COVID-19 patients (De Biasi *et al.*, 2020; Diao *et al.*, 2020; Mahmoudi *et al.*, 2020). However, PD-1, a T cell inhibitory receptor, can be upregulated by T cell receptor-induced activation, which likely reflects activation rather than functional exhaustion (Wherry and Kurachi, 2015; Singer *et al.*, 2016; Rha *et al.*, 2021). Other studies demonstrated that in COVID-19 T cells are activated rather than exhausted (Sekine *et al.*, 2020; Jung *et al.*, 2021; Rha *et al.*, 2021).

T cells in asymptomatic, mild and moderate COVID-19: SARS-CoV-2-specific T cells were functionally superior in asymptomatic individuals compared with symptomatic COVID-19 patients (Le Bert *et al.*, 2021). For example, T cells secreted higher levels of IFN-γ and IL-2 and a well-coordinated production of pro-inflammatory (IL-6, TNF-α, IL-1β) and regulatory cytokines (IL-10) than T cells from symptomatic COVID-19 patients. In a recent study, it was shown that pre-existing replication transcription complex (RTC: Nsp7, Nsp12, and Nsp13)-specific T cells were enriched and expanded in vivo in seronegative health care workers (SN-HCW, repeatedly remained negative by PCR, antibody binding, and neutralization tests) with abortive infection (confirmed by interferon-inducible transcript IFI27 in the blood, a robust early innate signature of SARS-CoV-2) (Swadling *et al.*, 2021). SN-HCW had memory T cells more frequently directed against the RTC, in contrast to structural protein-dominated responses in individuals with detectable infection. By contrast, the group with serologically confirmed infection showed no significant increase in RTC-specific T cells. The presence of virus-specific $CD8^+$ T cells has been associated with better COVID-19 outcomes (Grifoni *et al.*, 2020; Rydyznski Moderbacher *et al.*, 2020; Neidleman *et al.*, 2021; Sette and Crotty, 2021). Compared to S-protein, M/N-specific specific polyfunctional (IFN-γ, TNF, and IL-2) $CD8^+$ T cells were considerably higher in proportion in mild cases than in severe cases (Peng *et al.*, 2020). Another study showed that SARS-CoV-2 specific $CD4^+$ and $CD8^+$ T cells both were associated with less severe disease (Rydyznski Moderbacher *et al.*, 2020). Moreover, one COVID-19 patient resolved infection without hospitalization, who had no detectable neutralizing antibodies, but SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells were present. Another study showed that recovered individuals had elevated and increasing numbers of SARS-CoV-2-specific T cells capable of homeostatic proliferation compared with individuals who succumbed (Neidleman *et al.*, 2021).

T cells in severe/critical COVID-19: The number of $CD4^+$ and $CD8^+$ T cells were lower in severe COVID-19 cases than in moderate cases (Chen *et al.*, 2020). Lower frequencies of IFN-γ-secreting cells in both early stages (day 1–15) and late stages (day 15–30) were reported in moderate/severe COVID-19 patients compared with mild cases (Tan *et al.*, 2021). Moreover, one patient who died had no detectable IFN-γ-secreting cells until day 26 when stimulated with the different peptide pools. In contrast, studies have also shown that magnitude of T cells was not associated with recovery in critical COVID-19 cases (Schub *et al.*, 2020; Weiskopf *et al.*, 2020). SARS-CoV-2 specific T cells in severe COVID-19 may have restricted functionality despite high magnitude. For example, the total percentage of SARS-CoV-2–specific polyfunctional $CD4^+$ T cells (producing IFN-γ, TNF-α, and IL-2) was significantly lower in ICU patients than convalescents (Schub *et al.*, 2020) (Fig. 3). In contrast, it was also observed that $CD4^+$ and $CD8^+$ T cell responses of deceased or critical COVID-19 patients were robust and comparable or even higher than patients with moderate disease (Thieme *et al.*, 2020). A severe infection with a more robust immunogenic environment provided by a higher viral burden and inflammatory bystander activation might lead to a higher magnitude and functionality of the T cell (Thieme *et al.*, 2020).

Marked Lymphopenia is a more prominent feature in patients with severe COVID-19 (Tan *et al.*, 2020; Zhang *et al.*, 2021). It is believed that T cells might be more robustly recruited to the lungs in severe COVID-19. In this context, T cells in lungs and blood might be analyzed in parallel from the same patients at specific time points. Lung residential memory T cells (T_{RM}) were shown to be critical mediators for protection against secondary viral infections (Schenkel and Masopust, 2014). For example, Influenza A virus-specific lung T_{RM} provided potent protection against heterosubtypic influenza challenge, although transient (Pizzolla and Wakim, 2019). In the context of COVID-19 little is known about T_{RM}. However, studies have reported functional T_{RM} in the lung and nasal tissue (Liao *et al.*, 2020; Grau-Expósito *et al.*, 2021; Roukens *et al.*, 2021; Szabo *et al.*, 2021). In COVID-19 patients, airway T cells characterized by a resident memory T cells phenotype exhibited protective profiles (Szabo *et al.*, 2021). Higher frequencies of these cells were seen in younger individuals who survived the infection compared to older who succumbed (Liao *et al.*, 2020). Additionally, in severe cases of COVID-19, 'immunological misfiring' might result in maladapted immune responses associated with severe clinical outcomes and poor prognosis (Lucas *et al.*, 2020). Moreover, there are indications of alterations in T cell activation and/or differentiation. Firstly, increased expression levels of exhaustion markers (PD-1, TIM3, LAG3, CTLA4, NKG2A, and CD39) have been reported in patients with COVID-19, particularly in those with severe disease (De Biasi *et al.*, 2020; Diao *et al.*, 2020; Laing *et al.*, 2020; Song *et al.*, 2020; Zheng *et al.*, 2020a, 2020b). However, the expression of these receptors could also indicate recent activation (reviewed by Rha and Shin [2021]). Briefly, Rha *et al.* (2021) reported that PD-1 expressing S269-specific memory $CD8^+$ T cells were active and not exhausted in acute or convalescent cases, regardless of disease severity. Other studies reported hyper-activated $CD8^+$ T cells with increased cytotoxicity rather than inhibited in severe cases. For example, in mild, severe, and critical cases, peripheral $CD8^+$ T cells decreased in number with a compensatory increase in their cytotoxic potential (evaluated by granzyme A, granzyme B, and perforin expression) (Jiang *et*

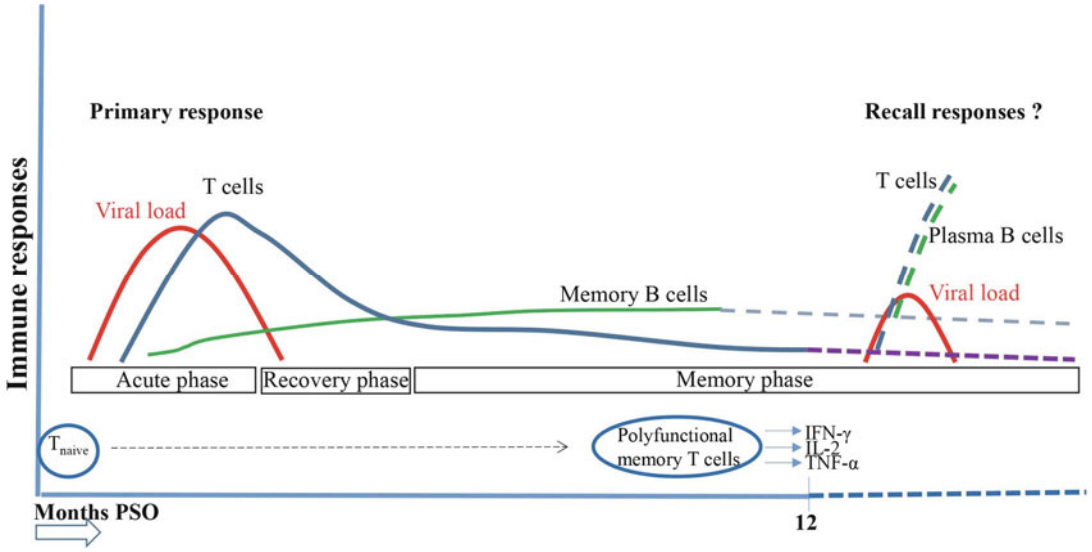
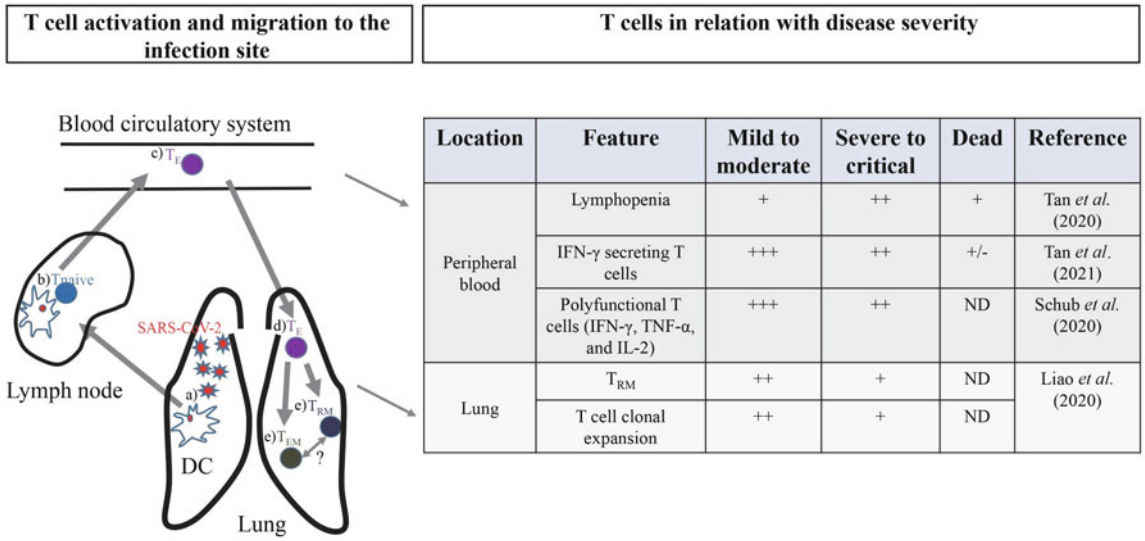


Fig. 2. A hypothetical model of cellular immune responses to SARS-CoV-2 infection. Finely tuned and effective induction of virus-specific T cells and antibody responses (B cell) leads to an effective clearance of SARS-CoV-2. $CD4^+$ and $CD8^+$ T cells peak in the acute phase of infection after which the frequency of cells decreases and maintains a stable level in the memory phase. Memory T cells have been reported to be polyfunctional, able to synthesize IFN-γ, IL-2 or TNF-α on re-stimulation. These cells can supplement memory B cells, which peak for at least 4–8 months before reaching a plateau, for effective formation of plasma cells. The memory phase cells might be strongly responsive to re-infection, ultimately limiting the viral replication and disease progression. Recall response? has not been evaluated yet in the context of COVID-19. Where dotted gray and purple lines represent that the specific memory B and T cells have not been evaluated after 8 and 12 months, respectively.

al., 2020). Another study, which employed single-cell RNA sequencing on nasopharyngeal and bronchial samples, reported that critical disease severity correlated with stronger interaction between epithelial cells and hyper-activated $CD8^+$ likely contributing to aggravated epithelial cell death (Chua *et al.*, 2020). Neidleman *et al.* (2021) reported that escalation of activated lung homing bystander $CD4^+/CD8^+CXCR4^+$ was associated with fatal COVID-19 outcomes. In contrast, a larger proportion of $CD8^+$ T cells with T_{RM} characteristics were present in BAL from patients with moderate disease compared to severe COVID-19 (Liao *et al.*, 2020). These studies demonstrate that peripheral blood and lung residential T cells might function in a coordinated manner against SARS-CoV-2 (Fig. 3). However, the exact differential role of T cells in asymptomatic, mild, moderate, and severe/critical cases remains to be elucidated.



Location	Feature	Mild to moderate	Severe to critical	Dead	Reference
Peripheral blood	Lymphopenia	+	++	+	Tan *et al.* (2020)
	IFN-γ secreting T cells	+++	++	+/-	Tan *et al.* (2021)
	Polyfunctional T cells (IFN-γ, TNF-α, and IL-2)	+++	++	ND	Schub *et al.* (2020)
Lung	T_{RM}	++	+	ND	Liao *et al.* (2020)
	T cell clonal expansion	++	+	ND	

Fig. 3. A proposed model of T cell responses to SARS-CoV-2 and relation with disease severity. On infection DCs uptake virus/viral particles during their migration to lung-draining lymph node a). Mature and activated DCs activate Tnaive to T_E b) and c). T_E migrate to the lung d). T_E can further differentiate into T_{RM} and T_{EM} e). Where ND = not determined, T_E = effector T cell, T_{EM} = effector memory T cell and T_{RM} = residential memory T cell.

Kinetics of T cells in COVID-19: SARS-CoV-2 T cells have been detected as early as Day 1 PSO (evaluated by MHC-tetramer staining) (Schulien *et al.*, 2021) with other studies (assessed by IFN-γ producing T cells by ELISpot) reporting 3–5 days PSO (Moderbacher *et al.*, 2020; Tan *et al.*, 2021). An early induction (< 10 days PSO) of SARS-CoV-2-specific T cells has been reported in milder cases (Tan *et al.*, 2021). $CD4^+$ and $CD8^+$ T cells show differential kinetics in the contraction phase: $CD8^+$ T cells display signs of progressive reduction after viral clearance while $CD4^+$ T cells were more stable during 1–3 months PSO (Rydyznski Moderbacher *et al.*, 2020). However, after an initial contraction phase (Tan *et al.*, 2021), polyfunctional (IFN-γ, IL-2, and/or TNF-α-secreting) T cells remained detectable for at least 6–12 months PSO (Breton *et al.*, 2021; Cohen *et al.*, 2021; Dan *et al.*, 2021; Le Bert *et al.*, 2021; Lu *et al.*, 2021). Polyfunctional T cells have been observed more frequently in convalescents with milder symptoms while severe and critical patients tend to have restricted functional T cells (1–2 months PSO) (Schub *et al.*, 2020).

On re-infection, memory T and B cells can be responsive and supplement each other in the viral clearance (Fig. 2). Immunological memory provides rapid protection against re-infection. Memory T cells can be classified as T residential memory (T_{RM}, $CCR7^+CD45RA^-$, reside at the site of infection), T central memory (T_{CM}, $CCR7^+CD45RA^-$, circulate in the blood and home in lymphoid organs), T effector memory (T_{EM}, $CCR7^-CD45RA^-$, circulate in the blood and home in non-lymphoid organs) and effector memory re-expressing CD45RA (T_{EMRA}, $CCR7^-CD45RA^+$, circulate in the blood) (Seder and Ahmed, 2003; Tian *et al.*, 2017; Gray *et al.*, 2018; Martin and Badovinac, 2018). In contrast to T_{RM}, which might be playing an important role in the clearance of SARS-CoV-2 (discussed in section 'T cells in asymptomatic, mild and moderate COVID-19'), several studies have been performed on peripheral blood T cell subsets in COVID-19 individuals. These cells are composed of naive (Tnaive), T_{CM}, T_{EM}, and T_{EMRA} phenotypes (Breton *et al.*, 2021; Cohen *et al.*, 2021; Dan *et al.*, 2021; Lu *et al.*, 2021; Schulien *et al.*, 2021), and early ($CD27^+CD28^+$) or intermediate ($CD27^+CD28^-$) differentiation phenotypes (Peng *et al.*, 2020). The presence of a minor Tnaive subset fraction (median, 3.9%) of $CD8^+$ T cells supports the notion that most of these cells have been efficiently primed during the infection (Schulien *et al.*, 2021). Another study reported that SARS-CoV-2-specific MHC-I $tetramer^+$ $CD8^+$ T cells exhibited an early differentiated memory phenotype ($CCR7^+CD127^+CD45RA^{-/+}TCF1^+$) in convalescents (Sekine *et al.*, 2020). This phenotype of cells was associated with stem cell-like properties. Of note, stem cell-like memory T cells (T_{SCM}) have the ability of self-renewal and multipotency to repopulate the broad spectrum of memory and effector T cell subsets (Gattinoni *et al.*, 2011, 2017). Moreover, T_{SCM} ($CCR7^+CD45RA^+CD95^+$) cells in COVID-19 convalescents displayed poly-functionality and proliferation capacity during a 10-month follow-up period (Jung *et al.*, 2021), suggesting that these memory T cells might be long-living. Moreover, in this study SARS-CoV-2-specific T cell memory was maintained regardless of disease severity. In a study comparing T cell responses in prolonged SARS-CoV-2 positive (PP) clinically recovered (CR) and healthy donors, the $CD8^+$ T_E/T_{EM} cell frequency and number was significantly lower in PP compared with CR patients (Yang *et al.*, 2021). The suppressed $CD8^+$ T cell differentiation in PP was likely to be associated with prolonged infection, demonstrating the importance of $CD8^+$ T cells in virus clearance. Moreover, SARS-CoV-2 N protein-specific IFN-γ^+ T cell response in the PP cohort was significantly weaker than that in the CR cohort.

Whether T cell kinetics vary among SARS-CoV-2 strains, and different proteins/epitopes induce different T cell kinetics remains to be evaluated. As described previously, Tan *et al.* (2021) reported that in mild cases, T cells specific for ORF7 and OFR8 were induced early and were more robustly detected in the early phase of infection. Nevertheless, these claims need to be evaluated in a larger population to reach a sound conclusion.

Summary of different methodologies used to evaluate the T cells in acute and convalescent individuals having asymptomatic, mild moderate severe or critical COVID-19 has been provided in Table 1.

T cells in vaccinated individuals: In mRNA (Sahin *et al.*, 2020), adenovirus vector-based vaccines (Swanson *et al.*, 2021), and protein subunit vaccines (Keech *et al.*, 2020) a Th1-skewed response with little to no Th2 cytokine profile has been detected, while Tfh and $CD8^+$ T cells have also been detected in vaccinated individuals (Sahin *et al.*, 2020; Koutsakos *et al.*, 2021; Painter *et al.*, 2021; Sette and Crotty, 2021). T cell responses in COVID-19 mRNA vaccinees showed memory phenotypes, with a preference for T_{CM} and T_{EM} for $CD4^+$ and T_{EM} and T_{EMRA} for $CD8^+$ T cells (Guerrera *et al.*, 2021; Tarke *et al.*, 2021), which were detectable for at least 6-months-PSO (Guerrera *et al.*, 2021). Moreover, vaccination also induced $CD4^+$ and $CD8^+$ T_{SCM}. T cell responses induced by vaccines are supposed to recognize SARS-CoV-2 variants (Geers *et al.*, 2021; Tarke *et al.*, 2021). For example, the $CD4^+/CD8^+$ T cell reactivity in vaccinated individuals was not significantly reduced by mutations in B.1.1.7 and P.1 (Jordan *et al.*, 2021; Tarke *et al.*, 2021). However, decreases of 14% and 22% were observed with the B.1.351 S-pools for $CD4^+$ and $CD8^+$ T cells, respectively. As discussed somewhere, multiple T cell epitopes are distributed across viral proteins including structural, non-structural, and accessory proteins which makes evasion of viruses from T cell responses more difficult than neutralizing antibody responses (Noh *et al.*, 2021). The vast majority of $CD4^+$ and $CD8^+$ T cell epitopes were not affected by mutations found in different SARS-CoV-2 variants (Tarke *et al.*, 2021). Neutralizing antibodies, on the other hand, tend to target a restricted protein domain exposed on the virus surface, such as the S-protein of SARS-CoV-2. Currently, mRNA, adenovirus vector-based, and protein subunit vaccines rely on the S-protein as immunogen. Vaccines with multiple targets, including but not limited to the SARS-CoV-2 S-protein, are currently being developed and should elicit broad T cell responses (Noh *et al.*, 2021). These include a) protein-based vaccine, incorporating multiple $CD4^+$ and $CD8^+$ T cell epitopes selected from SARS-CoV-2 M, S2, and N proteins (NCT04683224); b) DNA platform vaccine, expressing S and N proteins (NCT04715997) or S and ORF3a proteins (NCT-04673149); c) adenovirus vector vaccines expressing S and N proteins (NCT04843722 and NCT04563702); d) chim-

Table 1. Summary of immunological studies reporting role of T cells in SARS-CoV-2 in humans

Disease severity (n)	Disease state	Sampling time PSO/Post PCR-positive	SARS-CoV-2 peptide antigens	Assay used	Reference
Mild (14), moderate (4), and severe (2)	Convalescent	20–35 days	Predicted entire proteome	Flow cytometry a. AIM (CD4: $OX40^+CD137^+$, CD8: $CD69^+CD137^+$) b. ICS ($CD8^+$, IFN-γ, Granzyme B, TNF-α, and IL-10) c. Polarization of $CD4^+$ T cells ELISA of peptide stimulated PBMCs (IL-2, IFN-γ, IL-4, IL-5, IL-17A)	Grifoni *et al.* (2020)
Mild (9)	Convalescent	20–47 days	Overlapping E, S, and N	CyTOF with single-cell detection of antigen-specific cells	Neidleman *et al.* (2020)
Moderate to severe (10)	Acute	3-weeks after admission to ICU	Predicted entire proteome	1. Flow cytometry AIM (CD4: $OX40^+CD137^+$, CD8: $CD69^+CD137^+$) 2. ELISA of PBMC supernatants after stimulation with S	Weiskopf *et al.* (2020)
Mild (11), moderate (4)	Acute	4–56 days	Overlapping S, N, M and predicted entire proteome	Flow cytometry a. AIM (CD4: $CD40L^+OX40^+$, CD8: $CD69^+CD137/4\text{-}1BB^+$ b. Polyfucntionality CD8 (Granzyme B, TNF-α, IFN-γ)	Rydyznski Moderbacher *et al.* (2020)
Mild (2), moderate (3), severe (8), critical (90), and fatal (2)	Convalescent				
Asymptomatic (7), mild, moderate or severe	Acute (mild [10] and severe [17]) and convalescent (mild [40] and severe [26])	11–14 days	Predicted S, M, and N	Flow cytometry a. AIM ($CD69^+CD137^+$) b. Polyfucntionality CD4 (IFN-γ, IL-2, TNF-α, IL-17A, CD107a, Granzyme B, perforin) CD8 (IFN-γ, IL-2, TNF-α, CD40L, Granzyme B, perforin) c. Memory T cells (CCR7 CD127 CD45RA TCF1)	Sekine *et al.* (2020)
Mild (26)	Acute and convalescent	1–107 days	Predicted entire proteome	Flow cytometry Memory T cells Tnaive ($CD45RA^+CCR7^+CD27^+$) T_{CM} ($CD45RA^-CCR7^+CD27^+$) T_{EM} $CD45RA^-CCR7^{+/-}CD27^{+/-}$ T_{EMRA} ($CD45RA^+CCR7^-CD27^-$)	Schulien *et al.* (2021)
Asymptomatic (85) and symptomatic (mild and severe (75))	Convalescent	1–3 months	Overlapping N and M. 55 peptides covering the most immunogenic regions of S	1. IFN-γ ELISpot 2. Polyfucntionality ELISA: IFN-γ, IL-2, Il-6, TNF-α, IL-10, IL-1β, IL-12p70, and IL-4	Le Bert *et al.* (2021)
SN-HCW (55) Lab confirmed (71)	Asymptomatic and mild	16-weeks	E, M, N, S and RTC (SARS-CoV specific for IFN-γ ELISpot and SARS-CoV-2 specific for epitope mapping	IFN-γ ELISpot *In vivo* expansion of T cells	Swadling *et al.* (2021)
Mild (28) and severe (14)	Convalescent	At least 28 days	SARS-CoV-2 proteome except ORF1	1. IFN-γ ELISpot 2. Flow cytometry a. Functionality $CD4^+/CD8^+$ (IFN-γ, TNF or IL-2) b. Memory T cells T_{EM} ($CD45RA^-CCR7^+$) T_{CM} ($CCR7^+$ $CD45RA^-$) Early ($CD27^+CD28^+$) or intermediate ($CD27^+CD28^-$) differentiation phenotypes	Peng *et al.* (2020)
Mild (8), moderate/severe (4)	acute and convalescent	1 day to 2 months approx.	Overlapping S, N, M, ORF3a, ORF7ab, ORF8, Nsp7, Nsp13 ~40 peptides containing confirmed T cell epitopes of S	IFN-γ ELISpot	Tan *et al.* (2021)

Table 1. Continued

Disease severity (n)	Disease state	Sampling time PSO/Post PCR-positive	SARS-CoV-2 peptide antigens	Assay used	Reference
Critical (14)	Acute	Median 42.5 days	Overlapping S (N peptide sets) N, M, and the E	Flow cytometry Polyfunctionality CD4 (IFN-γ, TNF-α, and IL-2)	Schub *et al.* (2020)
Asymptomatic/mild (36)	Convalescent				
Moderate (32), severe (16), and critical (17)	Acute and convalescent	8–32 days	Predicted S and overlapping M and N	Flow cytometry Polyfunctionality $CD4^+$ ($CD137^+$ Granzyme B, IFN-γ, IL-2, IL4, TNF-α) $CD8^+$ ($CD137^+$ Granzyme B, IFN-γ, IL-2, IL4, TNF-α)	Thieme *et al.* (2020)
Moderate (3), severe (1) and critical (5)	Acute	7–25 days	_	Single-cell landscape of bronchoalveolar immune cells	Liao *et al.* (2020)
Mild (9), moderate (6), and severe (19, 6 died)	Acute = moderate and severe	0–76 days	Overlapping S	CyTOF with single-cell detection of antigen-specific cells.	Neidleman *et al.* (2021)
	Convalescent = mild	20–154 days			
Mild (13), severe (10), and critical (9)	Acute and convalescent	_	_	Flow cytometry Granzyme A and B, and perforin in $CD8^+$ T cells	Jiang *et al.* (2020)
Moderate (8) and critical (11)	Acute and convalescent	3–33 days	_	scRNA-seq on nasopharyngeal or pooled nasopharyngeal/pharyngeal swabs, bronchial protected specimen brushes and bronchial lavages	Chua *et al.* (2020)
Asymptomatic/mild/ non-hospitalized (33) and severe/hospitalized (8)	Convalescents	1.3 and 6.1 months	Overlapping S, N, M, and accessory protein 3a	Flow cytometry a. Memory T cells $CD4^+/CD8^+$: T_{SCM} ($CD45RA^+$ $CD95^+CD28^{+/-}CCR7^{+/-}CD27^+$), T_{CM} ($CD45RA^-CD27^+CCR7^+$) T_{TM} ($CD45RA^-CD27^+CCR7^-$) T_{EM} ($CD45RA^-CD27^-CCR7^-$) b. Polyfucntionality $CD4^+$ (IFN-γ, IL-2, TNF-α) $CD8^+$ (IFN-γ, IL-2, TNF-α) T_{EM} (IFN-γ, IL-2, TNF-α)	Breton *et al.* (2021)
Mild (180), moderate (62), and severe (12)	Acute and convalescents	Up to 8 months	E, S, M, N, and ORFs: 3a, 3b, 6, 7a, 7b, and 8	1. IFN-γ ELISpot 2. Flow cytometry a. Memory T cells $CD4^+/CD8^+$: T_{CM} ($CCR7^+CD45RA^-$) T_{EM} ($CCR7^-CD45RA^-$) T_{EMRA} ($CCR7^-CD45RA^+$) Analysis were restricted to positive responders b. Polyfucntionality $CD4^+$ (IFN-γ, IL-2, TNF-α, CD40L, Granzyme B) $CD8^+$ (IFN-γ, IL-2, TNF-α, CD40L, Granzyme B, perforin)	Cohen *et al.* (2021)
Asymptomatic/ mild (non-hospitalized [72]) and moderate/severe (hospitalized [10])	Convalescents	Up to 8 months	Predicted entire proteome	Flow cytometry a. AIM (CD4: $OX40^+CD137^+$, CD8: $CD69^+CD137^+$) b. Memory T cells\ $CD4^+/CD8^+$: T_{CM} ($CCR7^+CD45RA^-$) T_{EM} ($CCR7^-CD45RA^-$) T_{EMRA} ($CCR7^-CD45RA^+$)	Dan *et al.* (2021)

Table 1. Continued

Disease severity (n)	Disease state	Sampling time PSO/Post PCR-positive	SARS-CoV-2 peptide antigens	Assay used	Reference
Mild (14) and severe (15)	Convalescents	12 months	M, N, and S	Flow cytometry a. Memory T cells $CD4^+/CD8^+$: T_{CM} ($CCR7^+$ $CD45RA^-$) T_{EM} ($CCR7^-$ $CD45RA^-$) T_{EMRA} ($CCR7^-CD45RA^+$) b. Polyfucntionality CD4 (IFN-γ, IL-2) CD8 (IFN-γ, Granzyme B, and CD107a)	Lu *et al.* (2021)
Asymptomatic/mild (30) and symptomatic (moderate, severe, and critical [19])	Acute and convalescent	up to 10 months	Overlapping S, M, and N [a]S269	1. IFN-γ ELISpot 2. Flow cytometry: a. AIM (CD4: ($CD137^+OX40^+$, CD8: $CD137^+CD69^+$) b. Memory T cells $CD4^+/CD8^+$: T_{CM} ($CCR7^+CD45RA^-$) T_{EM} ($CCR7^-CD45RA^-$) T_{EMRA} ($CCR7^-CD45RA^+$) T_{SCM} ($CCR7^+CD45RA^+CD95^+$) c. Polyfucntionality $CD4^+/CD8^+$ T cells (IFN-γ, IL-2, TNF, and CD107a)	Jung *et al.* (2021)
Non-sever	Non-sever prolonged SARS-CoV-2 positive (PP, 46) and clinically recovered (CR, 41)	45–92 days	_	1. IFN-γ ELISpot (SARS-CoV-2 N, S1 and S2 proteins were used to stimulate PBMCs) 2. Flow cytometry Memory T cells $CD4^+/CD8^+$: T_E ($CD27^-CD45RO^-$) T_{EM} ($CD27^-CD45RO^+$) T_{CM} ($CD27^+CD45RO^+$)	Yang *et al.* (2021)

Where E = envelope protein, ICU = intensive care unit.
S = spike; M = membrane; N= nucleocaspid proteins.
ORF = open reading frame; Nsp = nonstructural proteins.
PBMCs = peripheral blood mononuclear cells; PSO = post symptom onset; RTC = replication transcription complex; T_E = T effector; T_{CM} = T central memory; T_{EM} = T effector memory; T_{EMRA} = Terminally differentiated effector memory; T_{SCM} = T stem cell memory; T_{TM} = T transitional memory.
SN-HCW = seronegative health care workers.
[a] S269 was used for MHC-I multimer staining.

panzee adenovirus and self-amplifying mRNA vector vaccines expressing S-protein and additional T cell epitopes (NCT04776317); e) synthetic modified viral vectored vaccine, encoding S and N proteins (NCT04977024); f) peptide vaccines, using $CD4^+$ or $CD8^+$ T cell epitopes (NCT04885361 and NCT04954469).

Future Perspective and Concluding Remarks

Currently, most of the vaccines adopt the S-protein as immunogen for inducing immune responses against SARS-CoV-2 in humans (Corbett *et al.*, 2020; Sahin *et al.*, 2020; Liu *et al.*, 2021). However, $CD8^+$ T cell immunodominant epitopes are also found in ORF1 and ORF3, their inclusion in the vaccines needs to be considered (Swadling *et al.*, 2021; Wellington *et al.*, 2021). Moreover, in humans recovered from mild cases, multiple cytokine (IFN-γ, TNF or IL-2)-producing $CD8^+$ T cells specific for M/N-proteins were higher in proportion compared with S-protein-specific cells, necessitating inclusion of M/N-proteins/epitopes for future vaccine studies (Peng *et al.*, 2020).

A large body of evidence has been accumulated on the role of T cells in coronavirus infections both in mice and in humans. However, the role of T cells in combating SARS-CoV-2 needs to be further investigated in depth in animal models due to difficulty and scarcity of human tissue samples for analysis. Additionally, whether the presence of SARS-CoV-2-specific T cells forebode a bad prognosis in severe and critical cases need to be carefully investigated.

Currently, cell-mediated immune responses against SARS-CoV-2 have been studied mostly in peripheral blood. As such, detailed analysis of the role(s) of tissue resident T cells in the context of SARS-CoV-2 infections would shed light on their relative importance in viral clearance and/or pathology.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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