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T cell control of SARS-CoV-2: When, which, and where?

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ABSTRACT

Efficient immune protection against viruses such as SARS-CoV-2 requires the coordinated activity of innate immunity, B and T cells. Accumulating data point to a critical role for T cells not only in the clearance of established infection, but also for aborting viral replication independently of humoral immunity. Here we review the evidence supporting the contribution of antiviral T cells and consider which of their qualitative features favour efficient control of infection. We highlight how studies of SARS-CoV-2 and other *coronaviridae* in animals and humans have provided important lessons on the optimal timing (When), functionality and specificity (Which), and location (Where) of antiviral T cells. We discuss the clinical implications, particularly for the development of next-generation vaccines, and emphasise areas requiring further study.

1. Introduction

The immune system consists of many interacting players that can act synergistically to protect against diverse pathogens. It is important to understand the relative contributions of the components of the immune response to identify individuals at particular risk from infection and to inform the design of immunotherapeutics and vaccines. However, most viral infections induce both innate and adaptive immune responses, and the strength of humoral and cellular responses is often correlated in magnitude. This complicates identification of dominant correlates of protection from infection or disease. When a specific component of the immune system can be correlated in magnitude or timing with a desired outcome, such as a mild course of infection or resistance to detectable infection, this is suggestive of a mechanistic role in protection; however, it may merely be an epiphenomenon [1]. It is also true that the relative contribution of immune components to protection after reinfection and vaccination may not be identical to those in primary infection. Moreover, redundancy within the immune system means that there may be more than one way to efficiently control an infection, with one arm compensating when another is deficient.

Much of the focus on immune protection in SARS-CoV-2 was initially on humoral immunity, since this is the arm that has been primarily harnessed by most successful preventative vaccines, and antibodies are relatively easy to measure in large populations. Neutralising antibody (nAb) levels have been correlated with vaccine efficacy against symptomatic SARS-CoV-2 infection with wild-type virus [2–4], but not consistently with COVID-19 disease severity during primary infection [5–9]. Taken together, a large body of literature reviewed elsewhere suggests that nAbs are particularly important in providing sterilising immunity to homologous virus re-exposure, but that they play less of a role in early viral clearance during primary infection [10].

An accumulating body of literature in humans and animal models has defined a critical complementary role for immune players beyond neutralising antibodies. The role for other responses has been further highlighted by SARS-CoV-2 variants that have escaped antibody neutralisation yet remain subject to a degree of immune control. The importance of an efficient early interferon response has been highlighted by the effect of naturally-occurring interferon antibodies on disease severity and underscored by the capacity of successive variants of concern (VoC) to manipulate cell-intrinsic immunity [11,12]. Temporal and qualitative features of non-neutralising antibodies have also been linked to outcome upon exposure [13] and in vaccine induced-immunity [14,15]. Antibody-dependent NK activation (ADNKA) and cellular cytotoxicity (ADCC) play a role in viral control, with the virus shown to antagonise this innate cellular response [16]. This appears to be predominantly mediated by nucleoprotein (NP)-specific antibodies. [17].

Multiple lines of evidence now support that T cells also play key roles both in controlling established infection and in termination of viral replication at its earliest stages [1,18], in particular during abortive SARS-CoV-2 infection[19]. However, much remains to be understood about the optimal T cell response to SARS-CoV-2.

In this review we will first briefly consider what can be learned about the importance of T cells in protection during SARS-CoV-2 infection through the study of animal models of infection and humans with

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specific immunodeficiencies. We will then focus on three key qualitative aspects of T cell immunity, considering ***when*** and ***where*** they can act, and ***which*** subsets and specificities optimise their efficiency.

2. What is the evidence T cells contribute to SARS-COV-2 control?

Difficulties quantifying T cell responses compared to serum antibodies mean the relative contribution of T cells to protection is likely underappreciated. High magnitude SARS-CoV-2-specific CD4, and to a lesser extent CD8, T cell responses have been correlated with reduced severity and asymptomatic primary infection [5,7,20]. An early high magnitude T cell response correlates with a lower peak viral load, rapid viral clearance, and better clinical outcomes, as discussed further below [7,21–24]. An important role for T cells in *prevention of disease* is suggested by lineages of the omicron variant of concern (VoC); these transmit easily due to their ability to evade a large proportion of nAbs induced by vaccination or infection with other strains [25,26], but cause markedly lower rates of severe disease. Even when considering differences in viral tropism, inherent virulence, and cross-reactive B cell responses, it is still evident that cross-reactive T-cells induced by previous infection with heterologous variants or vaccination retain recognition of emerging variants and are likely protecting against severe disease [27,28].

Our description of abortive SARS-CoV-2 infection [19], where T cell expansions are observed in the absence of antibodies in exposed individuals that do not develop PCR+ infections, indicates an additional role in *protection from overt infection*. T cell responses have also been linked to protection from infection in household contact study [29] and importantly, even in seropositive individuals the magnitude of IFNγ producing SARS-CoV-2-specific T cells, but not antibody measurements, correlated with protection from subsequent infection with delta or omicron variants [30].

Since these studies are correlative, we now consider what can be learnt about the role for T cells from animal and human studies where specific components are absent or are supplemented.

2.1. What can we learn from animal studies?

Animal studies provide direct and mechanistic evidence for the importance of T cells in blocking and clearing infection with a range of *coronaviridae*, independent of their role in supporting B cell and antibody responses. Depletion of CD4 or CD8 T cells inhibited clearance of the coronavirus Mouse hepatitis virus, despite an equivalent antibody titre, suggesting a dominant role for T cells in viral clearance [31]. Adoptive transfer of SARS-CoV-specific T cells to severe combined immunodeficiency disease (SCID) mice showed that they are necessary and sufficient for virus clearance and for protection from clinical disease in mouse-adapted coronavirus (MA15)-infected mice [32]. Notably, airway-resident virus-specific CD4 T cells, induced by intranasal vaccination, mediated protection against lethal MERS and SARS-CoV infection in mice [33] as discussed further below. A similar protective role for lung-resident influenza-specific CD4 T cells has been shown [34,35]. *Together, these studies demonstrate direct and indirect mechanisms by which T cells play a dominant role in viral control.*

Moving to SARS-CoV-2, Kingstad-Bakke et al. showed that in the absence of nAb, systemic lung-resident CD4 and CD8 memory T cells could clear beta variant (B1.351) infection without lung pathology[36]. SARS-CoV-2-mediated lung pathology was exacerbated in T cell depleted mice in another study [37]. A role for T cells in viral control has also been demonstrated in non-human primates. Transfer of purified IgG protected macaques from infection in a dose-dependent manner, but a higher Ab titre was required when CD8 T cells were depleted, suggesting a role for T cells in infection blocking when Abs have waned or are poorly matched to the viral antigen [38]. However, protection by pre-existing memory T cells alone was not tested. A loss of protection from Delta variant (B.1.617.2) infection when depleting CD8 T cells after vaccination with Ad26. CoV2. S (Wuhan hu-1 sequence) [39] has been described. Importantly, Wang et al. showed that mRNA vaccination could protect against Omicron BA.1 and BA.5 infection in B cell deficient mice, demonstrating the importance of IFNγ-producing T cells in mediating protection[40]. In contrast, Nelson et al. [41] only detected SARS-CoV-2-specific T cells in the lungs after viral RNA was undetectable and inflammation had resolved; a lack of temporal association between T cell induction and viral control was suggestive of innate control, with the caveat that low level T cell responses may not have been detectable by ICS and some specificities may have been missed using megapools of predicted epitopes. Differences in infective dose and route may explain differences in the contribution of T cells to protection in SARS-CoV-2. *However, as with other viral infections, T cell responses complement innate immunity and antibodies in controlling SARS-CoV-2 in the majority of animal models.*

2.2. What can we learn from humans with immunodeficiencies or immunotherapies?

Our observation that a proportion of healthcare workers could abort Wuhan hu-1 SARS-CoV-2 without any antibodies detectable on repeated testing provided strong support for the role of selectively expanded T cells targeting early viral proteins; moreover, their subtle IFN-inducible signature was not suggestive of a compensatory increase in this arm [19]. Further settings where immune control of SARS-CoV-2 can be unpicked in humans lacking antibodies include individuals undergoing B cell depleting immunotherapies or those with inborn errors of immunity.

Initial studies described a small number of patients with agammaglobulinemia (x-linked and autosomal recessive) having asymptomatic and mild infections [42,43]; however, a later meta-review of outcomes for 28 X-linked agammaglobulinemia patients demonstrated that hospitalisation was common, as was protracted infection [44]. Retrospective studies of the outcomes of a large number of recipients of B cell-depleting therapies (>400 rituximab [45] and >600 ocrelizumab-treated [46]) has demonstrated that the vast majority of their infections were mild and the case fatality rates were within estimates of the general public. Despite seroconversion being significantly lower in rituximab treated individuals and x-linked agammaglobulinemic patients, they can, however, mount equivalent, if not enhanced SARS-CoV-2-specific T cell responses to vaccination [47–49]. This is reminiscent of other settings where a high magnitude T cell response may compensate for a low nAb titre [50,51]. Thus, individuals with natural or therapy-induced B cell deficiency underscore the contribution of humoral immunity but also demonstrate that nAbs are not an absolute requirement for recovery from COVID-19.

Monoclonal nAbs targeting SARS-COV-2 spike protein have also had some efficacy when administered prophylactically or as postexposure prophylaxis [52,53] but their modest impact on viral load is indicative of a role of T cells, rather than circulating antibodies, in control of established infection. Overall, the study of donors lacking, or administered therapeutic, antibodies point to a key role for humoral immunity in blocking SARS-CoV-2 infection. *However, the fact that some individuals lacking humoral immunity have asymptomatic or mild SARS-COV-2 infection demonstrates that innate and T cell immunity can effectively control SARS-CoV-2 without an absolute requirement for antibodies.*

*Next we will consider **when** T cell need to act, **which** T-cell specificities and qualities have been linked to protection, and **where** they need to act to optimise efficient control of SARS-CoV-2.*

3. When do T cells contribute?

Some level of infection is required for virus-specific T cells to be recruited into the immune response as they recognise the presentation of viral peptides on MHC at the surface of infected cells. *T cells typically*

clear infected cells where neutralising antibodies failed to block viral entry and innate immune mechanisms could not completely shut down replication. Two important exceptions to this are the possibility of T cells recognising the incoming viral inoculum cross-presented by APC before target cell infection or T cells to early viral proteins aborting infection within target cells before initiation of the full replication cycle, discussed further below. However, the conventional view is that *T cells are important in restricting the extent of viral infection, thus modulating disease severity, and in terminating infection*; this role is supported by data in animal models as stated above, and by careful comparison between different severities of outcome upon infection.

An early T cell response is more commonly seen in individuals who have mild disease and who terminate infection quickly (Fig. 1). T cell responses in the early convalescent phase are broad, relatively high in magnitude, and polyfunctional in individuals who have mild disease [5,23] but they are delayed in those that develop severe or fatal disease [7,54,55]. In particular, individuals who are infected but are asymptomatic have a robust T cell response [5,20,56]. The timing of T cell responses has also been directly correlated with the time to viral clearance[57]. Although it is very difficult to identify and sample individuals immediately after exposure, some studies have observed CD4 [7,57,58] and CD8 T cell activation and expansion as early as 1–4 days post-symptom onset during primary infections [59]. A further study that managed to recruit individuals within the first few days of primary infection observed that early circulating SARS-CoV-2-specific T cells correlated inversely with nasal viral loads and systemic inflammation[60]. This is also the case for breakthrough infections in vaccinated individuals, where spike-specific T cells appear activated (CD71, PD-1, CXCR3, CCR5, ICOS, CD38) at the time of symptom onset, show expansion within 1 day, and peak in magnitude around day 6 [61], before serum neutralisation is boosted.

Few studies have been able to assess T cell responses prior to symptom onset or even PCR positivity to determine *exactly when T cells are engaged* after exposure to SARS-CoV-2 and how their early kinetics influence outcome of infection. Due to rapid recruitment, initiated before the UK went into its first lockdown, and intensive weekly monitoring (PCR and a panel of serology tests) we were able to sample vaccine and infection naïve health care workers in the weeks prior to symptom onset and PCR positivity during the first wave of SARS-COV-2 infections in the UK (March 2020). Whole blood transcriptomics identified signatures of proliferation and T-cell associated genes as the first signs of infection, synchronous with the interferon response [22], whilst systemic antibodies only became detectable 2–3 weeks later. This was validated using longitudinal TCR repertoire analysis, which showed clonal expansions peaking at the time of PCR positivity, but interestingly, as with the transcriptomic signatures of T cells, some clonal expansions were detectable in the week preceding PCR positivity [22]. Ki67+ CD8, and to a lesser extent CD4 T cells, were also detectable in the blood by flow cytometry at the time of PCR positivity. *Overall, we showed that T cell activation and expansion in the week preceding PCR positivity are characteristics of non-severe infections* [22]. Without a very high incidence of infection and widespread intensive monitoring, the very earliest kinetics of the immune response cannot be elucidated in prospective studies; however, the human challenge model represents a highly controlled situation in which repeated early sampling can be performed to give us a window into these early events[62]. In this model, activated T cells can be observed in the nasopharynx and blood 10 days post-inoculation [63].

Overall, a detectable SARS-CoV-2-specific T cell response in the blood within days of viral exposure (Fig. 1) is characteristic of well controlled infection and mild outcomes in primary and breakthrough infections.

3.1. Can T cells contribute to early viral clearance before infection is established?

There are now multiple studies pointing to an important role for T cells in also *blocking the establishment of a detectable infection*. It is not unexpected that on the continuum of severity of infection some exposures lead to low levels of infection that are controlled by the immune system without detectable viral replication (below limit of detection for PCR) and without the induction of antibodies (Fig. 1); however, the frequency of this type of abortive infection for a given virus and

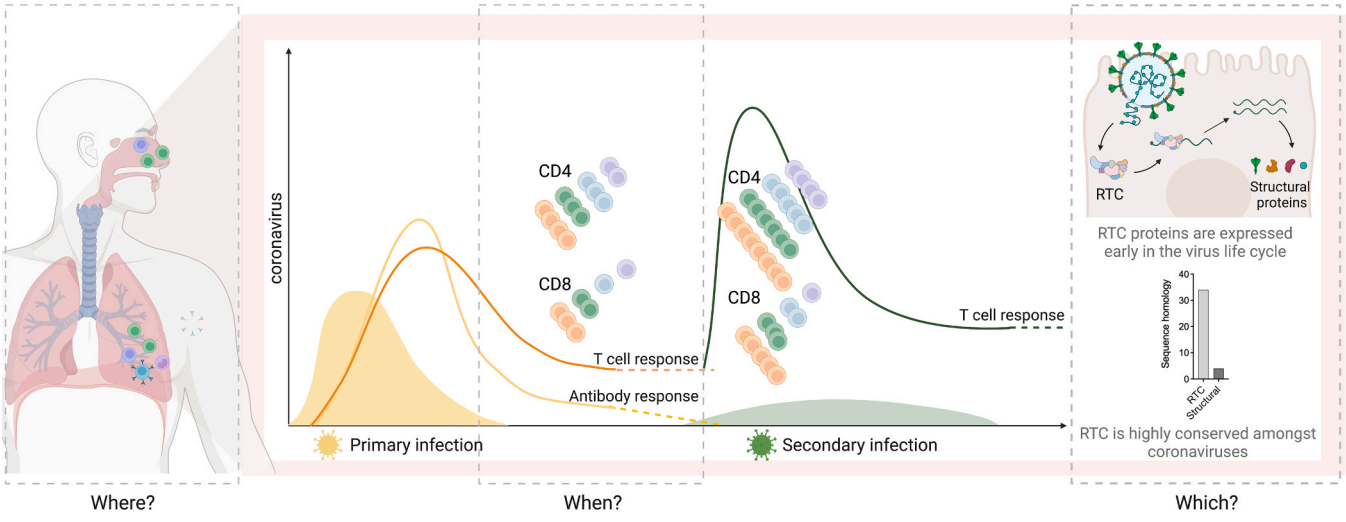

Fig. 1. Schema on Where, When and Which T cells optimally control SARS-CoV-2. Where: Mucosal T cell responses recognising SARS-CoV-2 have been identified in the upper and lower airways, and associated lymphoid tissue, before and during the pandemic; these tissue-resident responses are poised at the site of infection to play a dominant role in frontline protection. When: T cells in primary exposures are outpaced by rapid viral ramp-up so mainly contribute to clearing infection and limiting pathology. In secondary exposures, pre-existing memory T cells (from cross-reactive responses to related viruses or prior infection/vaccination) have higher precursor frequencies and more rapid expansion/effector function so can abort infection in the earliest stages, thereby blocking transmission. Which: SARS-CoV-2 infection or next-gen vaccines can generate multispecific CD4 and CD8 T cells targeting multiple viral proteins, contrasting with current vaccines only inducing responses to spike. T cells targeting early expressed and highly conserved RTC proteins are a correlate of abortive infection. T cells targeting the RTC may have a head-start at recognition of infected cells as ORF1ab is translated before the subgenomic RNAs of the structural proteins are made. The RTC is also much more conserved than structural proteins across variants of concern (VoC) and human coronaviruses (HCoV), providing a pool of more efficient cross-protective immunity. Created with BioRender.com.

population has previously been hard to determine.

For T cells to abort infection they would likely have to act very early after exposure. Where assessed, T cell responses can be seen *ex vivo* as early as the week leading up to PCR positivity [22]. We have reviewed the evidence that T cells can abort viral infections for SARS-CoV-2 and other viruses of global health importance (HIV, HBV, HCV, Influenza *etc.*) in detail elsewhere [1]. For SARS-CoV-2, we have shown that individuals who developed a blood transcriptomic signature of a viral infection, namely raised expression of the IFN-stimulated gene IFI27 [64], but who aborted the infection (remained seronegative and PCR negative) showed selective *in vivo* SARS-COV-2-reactive T cell expansions [19]. Importantly, pre-existing T cells that could cross-recognise SARS-CoV-2 were enriched prior to viral exposure in individuals who aborted infection in two cohorts (Medical students and laboratory staff, and health care workers) relative to individuals who went on to have a detectable infection; therefore, *pre-existing T cell responses correlated with protection from detectable infection.* This was also the case in a household contact study, which demonstrated that pre-existing cross-reactive T cells were significantly enriched in individuals who remained uninfected (PCR- and seronegative) despite household contact with an infected case, than those that were infected [29]. Enrichment of pre-existing memory T cells, primed and ready to rapidly respond to incoming virus, in individuals who resist developing infection that is detectable by highly sensitive PCR, is highly suggestive of a direct role for T cells in aborting infection. *Below we discuss the relevance to frontline cross-protection of the specificity of these memory T cells (Which) and their presence in the respiratory mucosa (Where).*

Vaccine studies also point towards a role for T cells in protection from detectable infection, with reduced infections being observable by day 10 post-vaccination, when T cells, but not neutralising antibodies, were detectable in the blood [21]. A single dose of mRNA vaccination shows measurable efficacy against symptomatic infection despite not inducing a detectable neutralising antibody response in a significant proportion of individuals, indicating that T cells and binding antibodies, which are detectable after a single vaccination, could be responsible for this efficacy [65].

An important question now is whether T cells play a role in protection from infection in a largely seropositive population with a mixture of high levels of previous infection and vaccination. An elegant study by Scurr et al. employed novel high-throughput whole blood assays to quantify the T cell response to SARS-CoV-2 structural proteins prior to the delta and omicron waves in the UK[30]. They showed that T cell responses were significantly higher in individuals who did not have symptomatic infections. The rates of infection were 43.2% in individuals with the lowest magnitude IFNγ+ T cell response before exposure contrasting with only 5.4% of individuals with high magnitude T cell responses over their 6-month monitoring period. The magnitude of binding antibodies to NP or spike and neutralising antibody titres did not correlate with protection from infection. This is highly suggestive of an important role for T cells in limiting infection even in seropositive individuals as the virus transitions to endemicity[66].

3.2. *Are pre-existing rather than de novo T cell responses required to abort infection?*

Memory T cells offer enhanced protection against reinfection relative to naïve T cells due to their clonal expansion, and therefore higher starting magnitude, and because they have differentiated to a memory state with a proteome, transcriptome and epigenome which is poised for more rapid proliferation and effector function. *De novo* priming of T cells by vaccination against antigens that have not previously been seen often takes ~2 weeks to induce a detectable T cell response in the blood [67,68]; it was therefore somewhat surprising that SARS-CoV-2 specific T cell responses were detectable so early in individuals naïve to both infection and vaccination.

The rapid emergence of T cells within a few days of SARS-CoV-2 exposure implicates boosting of T cell responses already present at high enough frequencies that they only require a few rounds of replication to reach detectable numbers. These could either be memory T cells primed by other pathogens, such as closely related coronaviruses, or represent *de novo* priming of naïve T cells that are of unusually high precursor frequency (Fig. 1). The latter explanation has been suggested by Milighetti et al. who characterised clonally expanded T cell receptors (TCR) through longitudinal analysis of non-severe infections [69]; they showed that rapidly expanding TCR are already enriched in naïve repertoires (and that this is also the case for early expanded LCMV-specific T cells). They could not attribute this high precursor frequency to previous expansion of these TCR by human coronaviruses (HCoV) exposure because where the epitope specificity was known for expanded clones, sequence alignment showed low sequence conservation with HCoV. Most TCR-epitope pairs and public clones have been described for spike and a limited number of structural proteins, which are known to be less conserved across *coronaviridae;* therefore, it remains plausible that the TCR of unknown specificity expanding early did predominantly target epitopes that are highly conserved across HCoV.

In all studies using sensitive T cell assays to detect memory but not naïve T cell responses (responsiveness to peptide in Enzyme-linked immunospot, activation-induced marker, or intracellular cytokine staining assays) *pre-existing SARS-CoV-2-reactive T cells* have been detected *ex vivo* in a large proportion of unexposed samples (pre-pandemic, pre-Aug 2019: ~10–50% depending on assay and viral targets included) [5,19,23,54,70,71]. In contrast, HCoV cross-reactive antibodies are much rarer and have not been associated with cross-protection [72,73]. Pre-existing cross-reactive T cells have been associated with more rapid viral clearance and protection from infection and disease for many other viral infections [1], with the most comprehensive data coming from influenza A [74,75].

Due to rapid recruitment and intensive monitoring we were also able to show *in vivo* expansion of pre-existing T cells in individuals who had abortive or lab-confirmed infections, demonstrating that pre-existing cross-reactive T cells are recruited into the immune response upon exposure[19]. Low et al. also identified T cell clones that cross-recognised SARS-CoV-2 and other HCoV, in particular, those that targeted the fusion peptide within S2 [76]. Pre-existing spike-specific immunity was additionally shown to enhance vaccine responses [77]. An HLA-B* 07-restricted epitope in NP that is conserved across HCoV [78] was the first individual epitope to be associated with protection from severe disease [79].

Antigen-experienced pre-existing T cells have therefore been shown to cross-recognise SARS-Cov-2 in vitro and in vivo and overall have been associated with stronger responses to vaccination, milder infections, and more rapid viral clearance (Fig. 1). Memory and naïve T cells interact and compete during an immune response and each antigen encounter, whether by vaccination or infection, will shape the immunity that persists to offer protection on reinfection [80,81]. It will be interesting now to see if widespread vaccination and infection has boosted or diluted out T cells targeting cross-reactive epitopes and whether there is a 'back--boosting' of protective immunity against the human coronaviruses.

4. Which T cells contribute?

Within the complex immune system T cells can play many diverse roles; as such, they vary not just in their specificity (the virus they target, the protein within that virus, the epitope within that protein and their TCR clonality within a response to that epitope) but also in their 'quality.' Quality encompasses a wide range of functions and characteristics which can imbue a T cell with more or less protective efficacy. Despite all the evidence for the important role for T cells in viral control, there is a paucity of data on exactly which T cells correlate with protection in viral infections. We cannot say exactly which type of T cell, which specificity, or which function is best at controlling a given virus, meaning we cannot tailor immunotherapies or vaccines to these ends.

Due to the unprecedented research efforts devoted to understanding immunity to SARS-CoV-2, a picture is starting to emerge of the qualities that may be particularly effective against this acute resolving respiratory virus.

Here we will briefly address data on the role of different T cell subsets and functions in SARS-CoV-2 before moving on to consider the importance of T cell specificity in more detail.

4.1. Which CD4 or CD8 subsets are important in SARS-CoV-2 control?

One fundamental division is into T cells that express the CD8 or CD4 co-receptor, which dictates whether they recognise viral peptides presented by MHC Class I or II (respectively). It also determines a whole suite of functions that are restricted or enriched within CD4 or CD8 T cells.

CD4 T cells can differentiate into a range of subtypes which perform helper functions (in particular Th1 for viral infections), such as instructing B cells (T follicular helper [Tfh]) [7,82,83], and CD8 T cells, [84,85]), recruiting innate cells [86], and initiating tissue repair [87], as well as direct effector functions such as the production of anti-viral cytokines (in particular IFNγ and TNF) and in some cases cytotoxicity [88]. Importantly, IFNγ+ CD4 T cells alone could protect mice from lethal SARS-CoV infection [33]; however, persistent IFNγ production alone, without co-production of the regulatory cytokine IL10 has been linked to a failure to resolve inflammation and severe pathology in mice [89,90] whilst optimal protection was provided by T cell populations that produced both IFNγ and IL10 [33]. This is recapitulated in human SARS-CoV-2 infection studies, with mild COVID-19 responses showing robust IFNγ and IL10 production [20], but prolonged IFNγ without IL10 being a characteristic of severe disease [91]. Tfh, a specialised subset that can home to the lymph nodes and assist in B cell maturation, are induced by SARS-CoV-2 infection and vaccination. In particular, Tfh activation during the acute phase of infection, measured by the expression of CXCR3, predicted convalescent antibody levels [61] and CCR6 + Tfh with the potential to home to the airways have been observed [82].

What is somewhat unusual in viral infections is the degree of enrichment of CD4 rather than CD8 T cell responses specific for SARS-CoV-2, observed in multiple studies after infection and within the pre-existing cross-reactive pool (Fig. 1)[19,23,24]. One explanation could be the greater propensity for CD4 T cell responses to be cross-reactive, due to greater flexibility in peptide binding to MHC class II and in TCR-MHC-peptide binding for the longer peptides recognised by CD4 T cells. Another possible explanation is the ability of SARS-CoV-2 to downregulate MHC class I which may limit CD8 T cell priming and expansion [92,93], leading to a relative increase in SARS-CoV-2-specific CD4 T cells.

Although often at lower magnitudes (reviewed in [94]), in most cases CD8 SARS-CoV-2-specific T cell responses are detected alongside CD4 responses after abortive or overt SARS-CoV-2 infection. As mentioned above, CD8 T cells have been associated with better outcomes of infection [7,79]. CD8 T cells, also known as cytotoxic T lymphocytes (CTLs) or killer T cells, main effector functions are the killing of infected cells and the release of anti-viral cytokines, in particular IFNγ, and are therefore considered the main direct mediators of viral clearance. Recent studies have also implicated CD8 T cells as innate-like sensors of infection that can orchestrate the recruitment and activation/maturation of other immune cells [95,96].

4.2. Which T cell Effector functions are important in SARS-CoV-2 control

The exact effector functions that are most efficient at controlling and clearing SARS-CoV-2 infection are not yet known. Many studies across diverse viruses (HCV, HBV, CMV, HIV, yellow fever) have shown that polyfunctional T cell responses are associated with greater viral control [97–100]. The majority of SARS-CoV-2-specific CD4 and CD8 T cells are polyfunctional, producing type I cytokines, (IFNγ, TNF) and the immunomodulatory cytokine IL2. Differences in the per cell production of cytokines has also been observed for SARS-Cov-2-specific T cell responses, with Le Bert et al. demonstrating a higher production per cell in asymptomatic infection [20] and Wang et al. showing a lower production in exposed individuals who remained seronegative (potential abortive infections; [101]. Implications for the efficacy of these responses during re-exposure are not known.

Highly proliferative T cell response may be expected to provide a more rapid recall response. Through careful comparison of hospitalized acute COVID-19 patients stratified by disease severity based on multiple clinical parameters, Riou et al. were able to show that poor polyfunctionality, in particular limited IFNγ production, and low proliferative capacity, characterised the CD4 T cell responses in severe disease, rather than a difference in the magnitude of the response [102]. In the study of household contacts who remained seronegative despite potential exposure, an enrichment of pre-existing cross-reactive IL2 producing T cells were seen, whereas differences in pre-existing IFNγ producing T cells were not significant [29]. This may indicate the importance of the pro-survival cytokine IL2 in SARS-CoV-2 control, or could be indicative of enhanced cross-protection by central memory-like CD4 and CD8 T cells that favour IL2 production.

It has been suggested that asymptomatic infection generates a less effective memory response than symptomatic infection. This may be the case for antibody induction [13,103], however, Le Bert et al. showed that the magnitude of the T cell response was comparable between asymptomatic and mild symptomatic infections, with the enrichment of polyfunctional T cells co-producing IFNγ and IL2, suggesting a robust memory response is generated that is likely to be as effective on re-exposure as the memory generated by symptomatic infection[20].

Overall, as with other viral infections, Th1-like effector functions dominate, with IFNγ and IL2 most commonly associated with control, but with an interesting potential role for IL-10 co-production in limiting pathology.

4.3. Which T-cell specificities are linked to protection?

A low magnitude but broad T cell response is characteristic of SARS-CoV-2 across all disease severities [5,19,104], with conservative estimates suggesting an average of 30–40 epitopes being targeted per person each for CD4 and CD8 responses[105]; this breadth is somewhat expected as SARS-CoV-2 has one of the largest genomes observed for a human RNA virus. T cell responses have been observed to all SARS-CoV-2 proteins [106–108], but the breadth and relative magnitude of responses to different regions (immunodominance) can vary widely, and has been linked to the severity of infection/outcome [7,19, 24,56].

4.4. Is multispecificity important?

The targeting of multiple viral epitopes by a T cell response (multispecificity) is expected to result in greater viral control as it increases the chance of recognising infected cells despite differential viral protein expression, limits the impact of escape at a single epitope and increases the chances of T cell memory recognising secondary infections. Viral escape has been described in selected SARS-CoV-2 T cell epitopes but the impact is likely to have been minimised by T cell responses to multiple other regions in these individuals [109–111]. For acute resolving infections such as SARS-CoV-2, a multispecific T cell response is likely most relevant for protection against re-infection with the range of viral variants. Few studies have directly assessed the impact of T cell breadth on outcome upon exposure to SARS-CoV-2, however, multispecificity has been associated with mild disease in at least one study [112]. It is important to note that T cell responses to SARS-CoV-2 are often near the limit of detection for T cell assays, meaning that multispecificity can be underestimated when T cell responses are subdivided by protein or protein subregion as they can fall just below the limit of

detection.

The immunodominance hierarchy by protein seen during the early convalescent period is similar between CD4 and CD8 T cell responses, with structural proteins being targeted most commonly - in particular spike, NP, membrane and ORF3a [5,24,71,106,113]. This is the case when all viral proteins are assayed, although there is a clear bias in the literature to analysis of structural proteins, resulting in a greater number of mapped epitopes in these regions [108]. Despite responses to spike often being the highest magnitude of any single protein, this still only accounts for ~25% of CD4 T cell responses. Within the non-structural proteins encoded in the ORF1a/b, NSP3, NSP4, NSP12 and NSP13 also make major contributions to the T cell response seen in the convalescent phase after mild infection [27]. Interestingly this hierarchy is mirrored in T cell responses to the endemic human coronaviruses, but with NSP2 and NSP12 being more dominant for NL63 and OC43 respectively [114]. Spike is one of the largest proteins of the virus and has a high level of expression from its subgenomic RNA, which may go some way to explaining its immunodominance.

SARS-CoV-2 infections are acute resolving in the majority of individuals; as such within host evolution due to T cell selection pressure is rarely seen. The global selection pressure is diluted across the virus as each HLA presents a specific set of viral peptides with little overlap between alleles, particularly in the case of MHC class I. T cell escape has, however, been observed in prolonged SARS-CoV-2 infections [115], as it has for persistent influenza A infection [116]. These cases demonstrate the importance of T cells in control and the ability of viruses that normally cause acute infections to escape given sufficient time.

Of note, all licensed vaccines induce multispecific spike-specific T cells that cross-recognise SARS-CoV-2 variants [27,28]. Tarke et al. demonstrated that an average of 90% of CD4 and CD8 T cell epitopes were fully conserved (100% sequence identity) across SARS-CoV-2 variants up to the emergence of omicron BA.1 and that mutations were not enriched in epitope sites [28,117]. However, for two sufficiently immunodominant epitopes presented by common HLA alleles, examples of viral escape in globally circulating viral variants across the pandemic have been described [109,111], suggesting T cells are influencing sequence viral evolution. However, the influence of viral constraint on mutations and the relatively short timeframe of the pandemic may have limited widescale T cell escape.

It is, however, also possible that a narrow response, more focused on highly protective epitopes may offer the same level of protection as a broad response containing T cells that are less effective at viral control. The removal of dominant T cell epitopes can lead to a stronger response to previously subdominant epitopes [118–121], which suggests SARS-CoV-2 vaccines may be improved by the removal of immunodominant epitopes that are not linked to protection or effective cross-recognition of variants. Detailed analysis of the protective value of T cell responses to specific viral proteins and individual epitopes is needed.

Through careful characterisation of the specificity of peripheral T cell responses and viral kinetics in the upper airways during the acute phase of SARS-CoV-2 infection, Eser et al. were able to demonstrate an inverse correlation between the magnitude of the NP-specific T cell response and viral clearance [60], which suggests an important role for this specificity of T cells in particular in early viral control. Although this is painstaking work, some details on the most efficacious T cell specificities are emerging. An elegant study by Peng et al. has demonstrated the protective value of an immunodominant HLA-B* 07:02-restricted epitope in nucleoprotein ($N_{105–113}$)[79] which has been confirmed elsewhere [59,122].

The widely used SARS-CoV-2 vaccines (*e.g.*, those of Moderna, Pfizer-BioNtech and AstraZeneca/University of Oxford) all contained whole spike protein. It is highly likely that the inclusion of immunogens other than spike will add another layer of protection. Previous infection appears to offer slightly better protection from reinfection than vaccination – this could be because of the immunity generated to viral proteins other than spike, and/or because the immunity is localised to mucosal sites where the virus is encountered, as discussed below in the '**Where**' section.

4.5. What is the protective value of T cells to highly conserved viral regions?

Having established early in the pandemic that pre-existing T cells that can cross-recognise SARS-CoV-2 are relatively common, attention then turned to what primed and expanded them. T cell cross-reactivity is predominantly a result of sequence similarity (with non-canonical binding also being described but much less common; [123]); each TCR has the ability to recognise a large range of closely related MHC-peptide complexes (estimated to be ~10^6 peptide-MHC combinations per TCR on average) [124]. It is expected that existing memory T cells that cross-recognise SARS-CoV-2 would have been primed by antigens with similar amino acid sequences to SARS-CoV-2. Evolutionarily related HCoV are likely to be the single biggest contributor to the pool of pre-existing cross-reactive T cells due to the large number of preserved and minimally divergent epitopes [19,24,59,71,125–127]. Epidemiological data have shown that recent common cold coronavirus (CCC) infection is associated with less severe outcomes of infection [128,129] that is not related to cross-reactive antibodies [130], but this has not been determined in all studies [131,132]. The frequent exposure of young children to common colds has been postulated to partially explain their relative resistance to symptomatic SARS-CoV-2 infection. A recent study supports this by showing that functional cross-reactive T cell memory to SARS-CoV-2 was established early in childhood, correlating with the frequency of responses against the HCoV OC43 in unexposed 2–6 year olds, peaked at age 6 and declined thereafter [133].

Antigens that are not related to coronaviruses can also induce T cells that cross-recognise SARS-CoV-2 peptides *in vitro*, such as peptides derived from CMV [134], Influenza A [135] and commensal bacteria [136]. The highest magnitude pre-pandemic response to cross-recognise SARS-CoV-2 observed in Bartolo et al. was surprisingly to a peptide in ORF8 which does not show sequence conservation in HCoV. Murray et al. have provided a comprehensive review of the impact of cross-reactive immunity on SARS-CoV-2 infection elsewhere [137].

Regions of high sequence conservation across viral variants and across related species may indicate functionally constrained areas within the viral sequence, which cannot incorporate mutations whilst retaining their functional role within the viral life cycle. In support of this, we showed that the proteins that showed the lowest genetic diversity (fewest mutations) over the pandemic across SARS-CoV-2 clades were the RNA-dependent RNA polymerase (RdRp, NSP12) and the helicase (NSP13), two essential proteins of the core replication-transcription complex (RTC[19]) (Fig. 1). Further, these were also the two most conserved proteins across HCoV, and across the whole *coronaviridae* family, including animal coronaviruses, suggesting functional constraint on mutation rates in these regions throughout the evolution of different species within the *coronaviridae* family [138]. An alternative hypothesis is that these essential non-structural proteins remain conserved due to a lack of selection pressure; positive selection by neutralising-antibodies has driven sequence change within the RBD of spike, however, non-structural proteins that are not present in the virion would not be under the same selection pressure[139]. Although it needs to be formally shown, it appears that NSP12 and NSP13 are more conserved than would be expected just by a lack of positive selection. We and others have also shown that these regions are immunogenic [19,113,126,140,141], inducing broad T cell responses, that were common in pre-pandemic samples. Most importantly we were able to show that pre-existing T cell responses to these core RTC proteins were selectively enriched before, and expanded further after, exposure to SARS-CoV-2 in individuals who resisted detectable infection [19].

Thus RTC-specific T cells from the pre-existing memory pool constitute a correlate of protection from overt infection [19], demonstrating the value of T

cells targeting antigens that are conserved across viral strains and species.

4.6. What is the protective value of T cells to early expressed proteins?

As discussed above, the relative magnitude, quality, and protective value of the T cell response can vary widely by viral protein. Some of these differences are driven by the *characteristics of the proteins they target*. For instance, whether a viral protein is only produced within an infected cell or whether it is part of the released virion, the timing of protein production within the viral life cycle, and the amount of the protein produced can all impact on presentation of the peptide and the concomitant T-cell response. These factors can also impact on which cells present the peptide, its dominance within the immunopeptidome and the timing of its presentation, both on professional antigen-presenting cells for priming and expanding responses, and on the infected cell for its recognition.

For example, the non-structural proteins of HIV (tat, rev, and nef) are expressed early within the virus life-cycle, therefore, T cells targeting these antigens may be able to recognise infected cells earlier than those targeting structural proteins. However, they are among the least immunogenic antigens during natural infection [142,143]. When encoded within highly immunogenic vaccines, strong T cells responses to rev, tat and nef can be induced, showing they are not inherently poorly immunogenic [144] and, importantly, vaccines encoding these early expressed proteins blunted the early peak viraemia after mucosal challenge with the highly pathogenic SIV mac251 [120,144]. Despite the rapidity of viral replication, when averaged across many infected cells it may be possible then that targeting early expressed proteins may lead to more control of early viral replication.

For SARS-CoV-2 it would be expected that the non-structural proteins of ORF1ab, the first viral protein to be produced in an infected cell, would also be presented first on APCs and infected cells. Additionally, ORF1ab encodes the proteins of the core replication-complex (NSP12 polymerase, NSP7 and NSP8 cofactors, and NSP13 helicase), which must be produced by coronaviruses before the subgenomic RNAs encoding the structural proteins, including spike, can be made and translated to protein (Fig. 1)[139]. Our finding that T cells targeting these early expressed proteins are enriched in abortive infections would be consistent with the possibility they are recruited into the immune response more rapidly to contribute to early control [19]. What is also striking is the relative lack of RTC-specific T cell induction when an infection is established. T cells targeting structural proteins dominate in detectable infection, particularly in those with the highest viral loads by PCR (lowest ct values), whereas those with the lowest viral loads (highest ct) had the most non-structural dominated response, reminiscent of abortive infection. RTC-specific T cells also dominated in individuals who tested PCR positive but did not generate detectable neutralising antibodies. *Overall, this may suggest that T cells preferentially target non-structural proteins produced before the full replicative cycle in early controlled infection, whereas full replication biases T cells towards the abundant structural proteins produced from subgenomic RNAs.*

SARS-CoV-2 completes its viral lifecycle *in vitro* very rapidly, therefore, differences in the timing of protein production from ORF1ab and subgenomic RNA (sgRNA) may be too small to have a significant impact on presentation and T cell recognition. However, if innate sensing of the virus were to restrain the lifecycle prior to sgRNA production, this would result in infected cells presenting ORF1ab peptides without yet having made the structural proteins. Yamada et al. showed that RIG-I can compete with the viral RdRp for binding to the viral genome and acts as a restraining factor, blocking the production of sgRNAs and downstream structural proteins in primary lung cells [145]. It is possible then that infected cells that are restrained at this early stage of the viral life-cycle can be recognised by T cells targeted proteins within ORF1ab but not T cells recognising epitopes within the structural proteins. It will be important to further investigate the *in vivo* relevance of RIG-I and other innate factors that can restrain viral replication in early control of viral replication and the impact this has on the recruitment of adaptive immunity.

5. Where do T cells contribute?

5.1. What is the protective value of airway-localised T cells?

For T cells to act quickly enough to protect against detectable infection, it is likely that some of the pre-existing cross-reactive memory responses would need to be situated at the site of viral inoculation and replication (Fig. 1). Memory T cells that reside in barrier tissues or organs (T_{RM}) have been described to provide immediate frontline immunity. In particular, T cells with the capacity to populate the different airway niches have proven essential in protection against respiratory infections. For example, the human lungs contain large pools of influenza-specific CD8 T_{RM} [146–149], and pulmonary CD8 [34,150] and CD4 [34,75] T_{RM} were demonstrated to mediate protection against influenza challenge in mice. Experimental human challenge with RSV induced high numbers of virus-specific airway CD8 T_{RM}, which correlated with less severe lower respiratory tract symptoms and reduced viral load [151]. The protective role of airway memory CD4 T cells has been demonstrated in mice after intranasal administration of a vaccine encoding a SARS-CoV CD4 T cell epitope that promoted protection against analogous virus infection and cross-protection against MERS in the absence of induction of antibodies [33]. This prior knowledge of the role of mucosal T_{RM} in other respiratory infections raises the question of what role local T cells have in CoV-2 protection following natural infection or after vaccination.

The distribution of T_{RM} over different body sites maximizes the chance of early pathogen recognition upon infection [152], but privileged location is not the only feature that makes them efficient in controlling infections. T_{RM} are transcriptionally programmed to rapidly respond to infections and their effector functions include the production of cytotoxicity-associated molecules, such as granzyme B and perforin, but also cytokines such as IFNγ and TNF, that can recruit other immune cells and influence the secretion of antiviral proteins by epithelial cells [153–156]. Lung CD8 T_{RM} had heightened polyfunctionality compared to their circulating or tissue-infiltrating counterparts after influenza infection [146,157], consistent with the capacity of T_{RM} to produce a large amount and variety of cytokines, besides being highly proliferative. Additionally, the capacity to persist long-term within tissues, considered a hallmark of T_{RM}, typically allows them to provide sustained protection against subsequent pathogen exposure. However, the T_{RM} pool in the airways has been documented to be less persistent than in a variety of other tissues including the skin [158], liver [159], and intestinal mucosa [160] and the decay of influenza-specific T_{RM} in the parenchyma and airways correlated with waning cross-protective immunity[161]. The increased attrition of the pulmonary T_{RM} pool is mainly described in mouse studies because of the difficulty of sampling these cells in humans longitudinally, but recent studies reveal that human airway T_{RM} can be more long-lived as we will discuss in the next section of this review.

5.2. What are the unique features of airway TRM?

Respiratory tract T_{RM} cells have been reported in the nasal mucosa and lungs, with the latter residing in the airways (epithelium) or parenchyma (interstitium) (Fig. 1)[162]. Respiratory tract T_{RM} share a common signature with T_{RM} in a wide range of other tissues, including reduced expression of proteins that promote tissue egress (S1PR1, CCR7 and CD62L) [163] and upregulation of proteins related to their ability to adhere to peripheral tissues (CD69 and the E-cadherin binding αE integrin (CD103) [164], as well as displaying specific transcriptional features that allow their survival and long-term retention at those sites [165,166].

T_{RM} in the distinct airway compartments have different phenotypic

and functional profiles, reflecting adaption to their local niche. For example, human airway CD8 T cells have greater expression of CD103 compared with their parenchymal counterparts [167]. Abrogation of T cell intrinsic TGFβ signalling results in impaired production of T_{RM} cells in the lung, whereas the formation of T_{RM} cells in the nasal cavity is unaffected[168]. Functionally, in comparison with CD8 T_{RM} localized to the airways, CD8 T_{RM} lodged in the parenchyma possess greater cytolytic function, expressing elevated levels of granzyme B as well as an increased capacity to synthesize IFNγ and TNF [169,170]. However, specific depletion of the airway fraction of memory CD4 T cells induced by an intranasal VRP-SARS-N vaccine showed that these were functionally superior to lung parenchyma-derived cells and were crucial for protection against both SARS-CoV-1 and MERS-CoV in mice in an IFNγ-dependent manner [33].

Compared to other tissues, the respiratory tract T_{RM} pools have been shown to wane faster, related to these cells being less long-lived, exiting the lungs or not being replenished. Airway and lung parenchymal CD8 T_{RM} display elevated levels of active caspases 3/7 and reduced levels of the anti-apoptotic molecule Bcl-2, being prone to cell death [161,166]. However, proliferating interstitial lung T_{RM} can function as a reservoir of responses to replenish declining airway T_{RM} [171]. Although murine lung CD4 CD69 + T_{RM} also decline, their decay was less rapid relative to CD8 T_{RM} in a model of asthma [172]. The local microenvironment of the lung, rich in oxygen and characterized by cellular stress and amino acid starvation, is not ideal to support long term T cell survival [166,173]; influenza-specific T_{RM} deposited in nasal tissue of mice declined less rapidly than lung T_{RM} [168]. Although T_{RM} were originally defined as having limited migratory capacity, they have recently been shown to be able to exit tissues and colonize draining LNs, which could help to explain the decay of pulmonary T_{RM}. It has been observed that T_{RM} exit the lungs *via* lymphatic vessels and relocate in the mediastinal LNs (medLNs) where they contribute to regional immunity and form a more durable memory pool, serving as a mechanism by which local T cells can contribute to systemic protection [174,175].

Pulmonary antigen encounter was required for recruitment of pathogen-specific effector T cells and T_{RM} establishment in the lung [176] and repeated antigen exposure by infection or vaccination could replenish the local T cell pool and help to reduce the attrition of airway T_{RM}. Higher persistence of lung CD8 T_{RM} and durability of heterologous protection was documented after repeated heterosubtypic influenza infections [177] or persistent local antigen exposure [178]. In humans, this repeated stimulation or cross-reactivity from a lifetime of infections and/or annual vaccinations may also account for the observation of donor-derived CD8 T_{RM} persisting for over a year post transplantation in the airways of lung transplant recipients [167].

5.3. Can airway T cells play a role in SARS-CoV-2 protection?

There is accumulating evidence for the formation of airway T_{RM} in SARS-CoV-2 infection, likely making a critical contribution to protection. Whilst nasal T cells may help limit viral replication at a site of SARS-CoV-2 entry, lower airway T cell responses could be critical to protect against life-threatening lung infection. SARS-CoV-2-specific T cells have been detected in nasal mucosa following infection by TCR sequencing [179] and by functional assays [180]. Virus-specific T cells have also been detected in lung tissue, particularly within the T_{RM} subset, at higher proportions than in matched blood in SARS-CoV-2 convalescent individuals, revealing both an enrichment of antigen-specific T cells in the lungs compared to the circulation and that these cells can persist for at least 10 months post infection [181,182].

Persistence of T_{RM} induced by respiratory coronavirus infection was also suggested by studies that identified pre-existing Sars-CoV-2 cross-reactive T cells, most likely induced by previous infections with seasonal HCoV. Compared to matched blood, superior frequencies of functional SARS-CoV-2–specific memory CD8 T cells were detectable in tonsils [183], a key lymphoid organ in the upper respiratory tract, and bronchoalveolar lavage (BAL) samples [140] obtained before the COVID-19 pandemic. In both studies, detection of pre-existing T cells correlated with the detection of HCoV-specific antibodies, suggesting more recent or repeated exposure to seasonal HCoV increased the persistence of cross-reactive T_{RM} in the airways and local lymphoid tissue.

Other studies have also provided evidence of lung T_{RM} during SARS-CoV-2 infection associating with subsequent improved control of disease or viral protection. A larger proportion of highly clonally expanded CD8 T cells with T_{RM} characteristics were present in BAL from patients with moderate compared to severe infection, although their antigen specificity was not analysed [184]. CD8 T_{RM} and CD4 T-helper-17 (Th17) cells in BAL underwent active expansion and displayed effector functions in mild COVID-19, whereas in critical COVID-19 they remained more naïve [185]. T cells in the airways exhibited activated, tissue-resident profiles and frequencies correlated with survival, younger age [186] and moderate disease [187] compared to their blood counterparts.

5.4. Need for mucosal challenge to induce local airway T cells?

Assessing local airway immune responses in humans is challenging and few studies have so far looked at T cell responses in the airways after vaccination with current intramuscular (i.m.) SARS-CoV-2 vaccines in humans. Although work from Ssemaganda et al. has reported expansion of CD69 +CD103 + CD8 T cells in the nasal mucosa after i.m. mRNA vaccination [188], other studies in humans report lack of local immunity after parenteral immunisation. SARS-CoV-2 specific T cells were detected in the nasal mucosa [180] and BAL [189,190] of vaccinated or unvaccinated individuals who experienced SARS-CoV-2 infection, but not in those that were vaccinated without a history of infection.

Animal studies also support that parenteral immunisation fails to induce T cells in the respiratory tract while airway mucosal immunisation elicits both systemic and local T cell immunity. Intranasal vaccine administration in BALB/c mice generated airway memory CD4 T cells that were more protective against challenge with mouse-adapted human coronaviruses (SARS-CoV and MERS) than those generated after systemic vaccination [33]. C57BL/6 mice immunised with SARS-CoV-2 Spike mRNA vaccine i.m. only showed antigen-specific CD4 and CD8 T cells in BAL following an intranasal boost with adenoviral vector [189]. Other groups have shown that mucosal immunization is necessary, not only to induce T cells in the airways, but also to achieve efficient protection against viral challenge. Also using a systemic priming/mucosal boost approach, Mao et al. showed that ACE2 Tg mice and Syrian hamsters injected with Spike mRNA-LNP i.m. prior to adjuvanted recombinant Spike protein or mRNA-LNP i.n. were protected against SARS-CoV-2 lethal challenge or lung pathology, respectively. Neither i.m. prime nor i.n. spike protein alone was sufficient to induce antigen-specific CD8 T cells in the lungs, BAL or nasal turbinates [191]. In another study, a single-dose intranasal immunization of BALB/c mice with trivalent adenovirus vector expressing spike, nucleocapsid, and a small section of RdRp (truncated NSP12) was superior to intramuscular immunisation in the induction of mucosal tissue-resident memory T cells, providing protection against mouse adapted SARS-CoV-2 [192].

Considering the vital function of the lungs in gas exchange, it is important to consider the capacity of T cells to mediate or exacerbate pathology. Some studies have reported a possible pathogenic role for lung T cells in SARS-CoV-2. Upregulation of proteins associated with ongoing cell death, epithelial damage, and tissue repair in post-COVID-19 airways correlated with increased numbers of activated tissue-resident CD8 T cells in BAL of patients with lung abnormalities [193]. During acute infection, non-hospitalized infected patients presented SARS-CoV-2-specific CD4 and, to less extent, CD8 T cells secreting IL-10, while hospitalized patients showed a bias towards an effector response characterized by IFN-γ and IL-4 secretion [181]. However, T_{RM} cells in lungs have been shown to express higher levels of inhibitory receptors

such as PD-1 and CTLA-4 than at other sites such as skin and intestine, suggesting they are also restrained, potentially minimizing unwarranted activation and local immunopathology [194,195] Moreover, induction of local T cells should be less risky in vaccination, where the lungs lack the pro-inflammatory local tissue environment implicated in promoting lung damage during COVID-19 [184,186].

6. Conclusions and Perspectives

A large body of work from animal and human studies now supports a contribution from T cells to the efficient control of SARS-CoV-2 infection. In addition to their classical role in helping to mop up virally infected cells that have escaped neutralising antibody-mediated protection, we argue that memory T cells can also play a frontline role in shutting down infection in its earliest stages, even in the absence of antibodies. Analysis of this prototypic T cell-mediated protection can provide vital clues to guide the optimisation of next-generation vaccines, aiming to induce T cells with efficient timing, specificity, and location.

Although current SARS-CoV-2 vaccines do induce some spike-specific T cells, they have not been designed for optimal T cell generation in order to enhance their efficacy against current and future VoC or new zoonotic transfers. The fact that donors with B cell deficiencies can still mount effective T cells, highlights this group as one that should particularly benefit from a T cell-focused SARS-CoV-2 vaccine. This is reinforced by a recent macaque study showing control of SARS-CoV-2 infection independent of neutralising antibodies by a non-spike vaccine (containing N, M and E) [196], although Fc-dependent antibody function could also have contributed.

Pre-existing cross-reactive memory T cells provide more rapid clonal expansion and effector function which we have shown can abort infection before virus becomes detectable, thereby holding the potential to block infection, disease, and onward transmission. Whilst many donors will now have a pool of multispecific SARS-CoV-2-reactive T cells from infection with this virus as well as related HCoV, boosting of the most variant-resistant specificities could be further enhanced by targeted vaccination. For example, RTC-specific T cells are not efficiently induced by overt SARS-CoV-2 infection, but are instead a correlate of abortive infection that could provide variant cross-protection if expanded efficiently by vaccines.

A further way to enhance the efficiency of vaccine-induced T cells is to target them to the respiratory mucosa, where they can provide frontline protection at the site of viral replication. The balance of evidence supports airway T_{RM} having a protective rather than pathogenic role in SARS-CoV-2, providing clear rationale for their induction or boosting by mucosal-delivered vaccines. Attempts at mucosal vaccination against SARS-CoV-2 in humans have started, but studies are at early stages [197]. One study with results already published showed that SARS-CoV-2 negative adults immunised with aerosolised adenovirus vector-based Spike vaccine showed comparable induction of systemic antibody and cellular immune responses to i.m. injection but requiring only a fifth of the vaccine dose[198].

In conclusion, more work is required to define the detailed specificities, memory phenotypes, effector functions and localisation of the most efficient T cells against SARS-CoV2; however there is already strong rationale for further development of vaccines aiming to induce airway-resident CD4 and CD8 memory T cells targeting highly conserved regions of SARS-CoV-2.

Author contributions

MOD, MKM, and LS researched and wrote this review jointly.

Conflicts of interest

The authors declare no competing interests.

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Data Availability

No data was used for the research described in the article.

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