Science Immunology

PERSPECTIVE

Cite as: A. C. Karlsson *et al.*, *Sci. Immunol.* 10.1126/sciimmunol.abe8063 (2020).

CORONAVIRUS

The known unknowns of T cell immunity to COVID-19

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Tremendous progress has been made in understanding the role of T cell immunity in acute and convalescent COVID-19 infection. Here we shed light on the "known unknowns" of pre-existing and acquired T cell responses in relation to acute and convalescent SARS-CoV-2 infection.

INTRODUCTION

The broad clinical spectrum of COVID-19 indicates widespread intraindividual differences in the host immune defense against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The underlying cause of disease heterogeneity is probably multifactorial. However, a rapid early host response is likely critical to generate control of SARS-CoV-2 viremia before spread to the lower respiratory tract and onset of damaging hyperinflammation. In this regard, the literature is full of examples where functional T cell responses can provide early control of acute viral infections, including SARS-CoV and MERS-CoV (*1*, *2*). Although multiple studies have indicated that T cells play a role in the early immune response to SARS-CoV-2 and can generate a functional memory pool, there are still multiple unanswered questions in the field (Box 1). Here, we summarize and speculate on a specific set of questions related to T cell immunity against respiratory viral infections, with a focus on COVID-19 severity, immunity, long-term consequences, and vaccination (Fig. 1).

T CELLS IN ACUTE SARS-COV-2 INFECTION

T cells are critical to generate early control and clearance of many viral infections of the respiratory system (*3*). Recent studies in transgenic mouse models provided evidence that T cells are also important for viral clearance and disease resolution after SARS-CoV-2 infection (*4*). As such, it is not surprising that T cell activation has emerged as a hallmark of acute COVID-19; probably as a consequence of an early SARS-CoV-2-specific cellular immune response (*5*–*9*). Although early T cell responses may play a critical role in dampening disease severity, there are also reports describing a dysregulated and unchecked T cell activation pattern in severe cases (*10*–*12*). Increased T cell activation in severe cases likely reflects increased antigen levels in the respiratory system, but whether the early T cell response reaches a state of exhaustion in subjects with severe hyperinflammation remains to be determined. Furthermore, given that COVID-19 is a disease of the respiratory tract it will be important to define if early detection of T cell activation in blood correlates with tissue-specific events. For instance, will delayed detection of SARS-CoV-2-specific T cells in blood reflect the later onset of cellular immunity in the respiratory tract or are these two compartments independent of each other in relation to disease severity?

If elicitation of an early T cell response would be beneficial to dampen COVID-19 severity, what might be the underlying causes and correlates of an early versus late onset of SARS-CoV-2-specific T cell activity? Old age and male sex are both associated with increased risk of COVID-19 complications. Interestingly, females seem to mount a somewhat stronger T cell activation following SARS-CoV-2 infection (*13*) and disruption of T and B cell coordination has been implicated in elderly patients with severe COVID-19 (*14*). On the other end of the age spectrum, decreased frequencies of IFN-γ^+CD4$^+$ and CD25$^+$CD4$^+$ T cells have been described in hospitalized pediatric patients, who have shorter lengths of stay compared with their adult counterparts (*15*). In conjunction with age and sex, host and viral factors probably also play a role in the early immune defense and coordination of the early SARS-CoV-2-specific T cell response. For instance, SARS-CoV-2 has mechanisms to antagonize proinflammatory signals, particularly type I IFN (IFN-I) signaling (*16*, *17*). IFN-I proteins are key inflammatory mediators to initiate antiviral defense, from which viral evasion might lead to a delayed clearance of SARS-CoV-2 (*4*). This is supported by the observation that inborn errors of immunity and autoantibodies that diminish IFN-I activity are more commonly detected in patients with severe COVID-19 (*18*, *19*). Concordantly, the early expansion and differentiation of antiviral T cells are dependent on the direct action of IFN-I. Given that activated T cells from older individuals exhibit reduced responses to IFN-I, it is tempting to speculate that higher risk elderly persons experience delayed activation of SARS-CoV-2-specific T cells that may lead to reduced clearance of the virus and

exacerbated COVID-19 severity. Collectively, more data are needed from mechanistic studies in animal models as well as large cohort studies on males and females in different age groups to identify beneficial and detrimental viral and host factors that have an impact on the early T cell response against SARS-CoV-2.

LONGEVITY AND MEMORY T CELL FORMATION

Generation of memory T cells can provide lifelong protection against pathogens (*20*). Previous studies have demonstrated that SARS-CoV- and MERS-CoV-specific T cells can be detected many years after infection (*21–23*). Likewise, SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cells are distinguished in a vast majority of convalescent donors (*7*, *9*, *21*, *24–27*). Studies using peripheral blood have reported stronger SARS-CoV-2-specific $CD4^+$ than $CD8^+$ T cell responses in most subjects. However, it is well established that $CD4^+$ T cells experience a higher propensity to recirculate between tissues and blood than $CD8^+$ T cells. As such, whether SARS-CoV-2-specific $CD4^+$ T cell responses also predominate in tissues, and particularly at barrier sites close to the epithelium, needs to be confirmed through studies on the upper and lower respiratory tract.

Similar to the $CD4^+$ T cell polarized response to many other viral infections, SARS-CoV-2-specific $CD4^+$ T cells mainly possess a Th1 or circulating T follicular helper (T_{FH}) cell phenotype (*7–9*, *14*, *28*). Circulating T_{FH} differentiation seems to be impaired in certain patients with severe COVID-19 (*11*, *29*) and recent analysis of postmortem lymph nodes and spleen samples showed an absence of germinal centers along with a defect in $Bcl6^+$ T_{FH} differentiation in deceased COVID-19 patients (*30*). Whether these consequences are due to sampling from postmortem patients remains unknown, but further studies are needed to clarify whether T_{FH} cell formation is impaired by SARS-CoV-2 and could have an impact on declining antibody responses in specific convalescent donors. Furthermore, more mechanistic studies are needed to understand if memory T cells can generate protective immunity to lethal challenge with SARS-CoV-2, as previously demonstrated in SARS-CoV and MERS-CoV models (*1*, *2*), in the presence or absence of high titers of neutralizing antibodies. Likewise, longitudinal human studies will also inform us of whether functional memory T cell responses are present many years after SARS-CoV-2 infection and correlate with protection from reinfection.

CROSS-REACTIVE T CELLS

Several studies have demonstrated the presence of $CD4^+$ and to a lesser extent $CD8^+$ T cells recognizing SARS-CoV-2 peptides in a significant proportion of unexposed individuals (*7*, *21*, *24*, *26*, *31*). Mapping of SARS-CoV-2 epitopes in unexposed blood donors revealed pre-existing T cell immunity, potentially induced by seasonal human coronaviruses (HCoVs) causing common colds (*27*, *32*). This is supported by a relatively high amino acid similarity between recognized SARS-CoV-2 epitopes and seasonal HCoVs such as HCoV-OC43, -HKU1, -229E and -NL63. The presence of cross-reactive cellular immune responses in the population generates an obstacle to the use of T cell-based assays to track SARS-CoV-2 infection rates in blood donors. Given that antibodies do not result in the same degree of cross-reactivity as T cells and are consequently easier to use in clinical diagnostic settings, serology will likely be a better readout for tracing the infection rate in the society. Nevertheless, more thorough studies are needed to better understand the full spectrum of cross-reactive versus newly-induced SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T cell responses.

A key question in the field is whether pre-existing T cell responses influence the severity of COVID-19. Pre-existing SARS-CoV-2-specific T cells are unlikely to provide sterilizing or herd immunity but may allow the host to bypass immune evasion mechanisms, for instance evasion from IFN-I, and generate early pressure on the virus. This concept is supported by studies in mice showing that airway memory $CD4^+$ T cells recognizing a conserved SARS-CoV epitope provided protection from related CoVs (*1*). Similar scenarios in which pre-existing T cells may provide earlier viral clearance and thus less severe symptoms have been proposed elsewhere (*33*). Here, the level of conservation between antigens may have a substantial impact on whether pre-existing T cells are beneficial or detrimental for the host. On the other hand, the concept of "original antigenic sin", in which earlier induced antibody or T cell responses influence the response against future viral infections, needs further evaluation (*34*). If pre-existing T cells are less effective in clearing viral infection upon activation but contribute to systemic and permanent increase in inflammatory signals, it might lead to increased hyperinflammation and COVID-19 severity. In a first analysis, comparing T cell responses against SARS-CoV-2 and HCoV sequences did not find any evidence of "original antigenic sin" (*32*). Again, the level of conservation of targeted epitopes is likely to impact the outcome, and further evaluation of this concept is needed. Collectively, further animal studies and human studies done before and after SARS-CoV-2 infection are needed to define the biological relevance of pre-existing T cell responses and their role as friends or foes in host defense against SARS-CoV-2.

SARS-COV-2-SPECIFIC T_{RM}

Resident memory T cells (T_{RM}) are a distinct memory T cell lineage. These cells reside within tissues, do not recirculate to peripheral blood, and have been defined as local sentinels mediating rapid protection from reinfection (*35*). In fact, a vast majority of T cells in nonlymphoid tissues, such

as the respiratory tract, are considered to be T_{RM} (*36*). In terms of respiratory infections, there is a growing body of literature demonstrating that T_{RM} can provide protection against severe pulmonary disease (*37*, *38*). Likewise, airway $CD4^+$ T cells can generate cross-reactive immunity between human and bat coronaviruses (*1*), emphasizing that cross-reactive T cells in the respiratory tract can provide protection from lethal challenge with pathogenic coronaviruses. Whether cross-reactive T_{RM}, induced by seasonal coronaviruses, can block transmission of SARS-CoV-2 from the upper respiratory tract to the lung and thereby attenuate severe COVID-19 remains unanswered. This scenario, where T_{RM} block the spread of viral disease from upper to lower respiratory tract, has been demonstrated in influenza A infection (*37*) and might account for partial immunity of secondary infection with heterologous strains (*39*, *40*). Furthermore, whether SARS-CoV-2-specific T_{RM} are induced after COVID-19 and whether these cells will provide protection in the long term also remains unknown (*41*). Although certain studies in mice have suggested that T_{RM} in the lung are short-lived (*42*), there is evidence that their counterparts in the upper respiratory tract persist with minimal decay (*37*) and for more than a year in human lung (*43*). Altogether, there is currently no evidence supporting the provision of "sterilizing immunity" by T_{RM}, but data presented above suggest that T_{RM} could facilitate rapid control of upper respiratory tract SARS-CoV-2 infection, replication, and spread. In this regard, further work in animal models may provide evidence for whether local immunity mediated by T_{RM} can achieve this type of immunity.

LONG COVID

A substantial number of COVID-19 patients experience heterogeneous symptoms that persist over a month and onward (*44*–*46*). This heterogeneous phenomenon is being referred to as "long COVID" and affects around 10% of all COVID-19 patients (*44*, *45*). Many symptoms can be attributed to persistent tissue damage in severe COVID-19. Nevertheless, the fact that many individuals with milder COVID-19 symptoms also experience chronic lingering symptoms, involving the cardiovascular, nervous, and respiratory systems, indicates that persistent immune activation and/or inflammation may play a role in long COVID. Multiple mechanisms are probably involved in this condition and whether T cells play any role in long COVID is unknown. The higher incidence of long COVID in females than males, similar to autoimmune diseases (*47*), raises the question of whether T cells orchestrate long COVID through similar mechanisms as in autoimmune or inflammatory conditions (*48*, *49*). One hypothetical underlying mechanism behind autoimmune-related conditions after COVID-19 could be molecular mimicry, given that HCoV-specific T cells can cross-react to myelin in multiple sclerosis patients (*50*). Whether SARS-CoV-2-specific T cells have the ability to react against self-antigens remains to be determined. In line with a possible effect of HLA type on COVID-19 susceptibility/severity (*51*, *52*), we believe that larger genetic studies are needed to clarify if HLA or other immune-related genes are associated with an increased risk of developing long COVID.

T CELLS IN VACCINES

Based on the uncertainty of whether cross-reactive T cells or antibodies will provide protective or long-lasting immunity to COVID-19, it will become absolutely critical to administrate a safe and effective vaccine to the population to reach broad immunity and break the negative spiral of new infections. Ongoing vaccine efforts mainly target B cells to promote the induction of neutralizing antibodies (nAbs) against SARS-CoV-2 (*53*, *54*). Although the induction of anti-spike nAbs is the key component for an effective SARS-CoV-2 vaccine, it is well-known that T cells, and in particular T_{FH} cells, are critical to generate antibody-producing plasma cells and long-lived memory B cells. In COVID-19 patients, high nAb titers correlated with strong $CD4^+$ T cell responses, and the lack of functional T_{FH} cells reacting against SARS-CoV-2 was shown to be detrimental (*11*, *29*, *30*). Preliminary results from the two major mRNA vaccine trials in humans have demonstrated potent Th1 responses (*55*, *56*). However, previous studies have reported strong T_{FH} responses against certain mRNA vaccines (*57*), and future trials should therefore include other activation induced markers, such as CD40L and/or CD200, in addition to IFN-γ ELISPOT assays to understand if potent B-helper mechanisms are induced by the current vaccine regimens. Other outstanding questions are whether vaccine-induced T_{FH} responses will be equally induced in all age groups and how long these responses will persist in blood and vaccination site-draining lymph nodes. A final issue to consider is whether high quantities of vaccine-induced $CD8^+$ T cells at local sites need to be elicited by future vaccine candidates. If the initial group of vaccines in clinical trials that are primarily focused on generating an effective nAb response provide recipients with long-standing protection, it may not be necessary to invest in such efforts. However, if problems emerge in the vaccinated population with breakthrough infections, waning antibody levels after vaccination, and/or the emergence of new viral strains, it would be wise to reconsider vaccine approaches specifically designed to induce functional $CD8^+$ T_{RM} responses in the upper respiratory tract.

SUMMARY

Collective efforts have greatly enhanced our scientific understanding of T cell responses against SARS-CoV-2 but many unknowns remain to be resolved. Although it is clear that T cells play a central role in generating early control and

clearance of many viral infections, their role in SARS-CoV-2 infection is only starting to be revealed. Specific T cells may even have a detrimental impact on the clinical outcome and contribute to long COVID symptoms. Currently, there is a need for deeper analysis using both animal models and longitudinal follow-up studies of large patient cohorts to define the beneficial versus detrimental aspects of SARS-CoV-2-specific T cells in acute, convalescent and vaccine settings of COVID-19.

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Acknowledgments: Funding. A.C.K. was supported by the Swedish Research Council, the Karolinska Institutet, and The Center for Innovative Medicine. M.B. was supported by the Swedish Research Council, the Karolinska Institutet, the Jeansson Stiftelse, the Åke Wibergs Stiftelse, the Swedish Society of Medicine, the Swedish Cancer Society, the Magnus Bergvalls Stiftelse, the Lars Hiertas Stiftelse, the Swedish Physician against AIDS Foundation, the Jonas Söderquist Stiftelse, and the Clas Groschinskys Minnesfond. **Author contributions:** A.C.K., M.H. and M.B. contributed to writing and drafting the illustration. A.C.K. and M.B. edited the manuscript. **Competing Interests.** The authors declare that they have no competing interests.

Published First Release 18 November 2020
10.1126/sciimmunol.abe8063

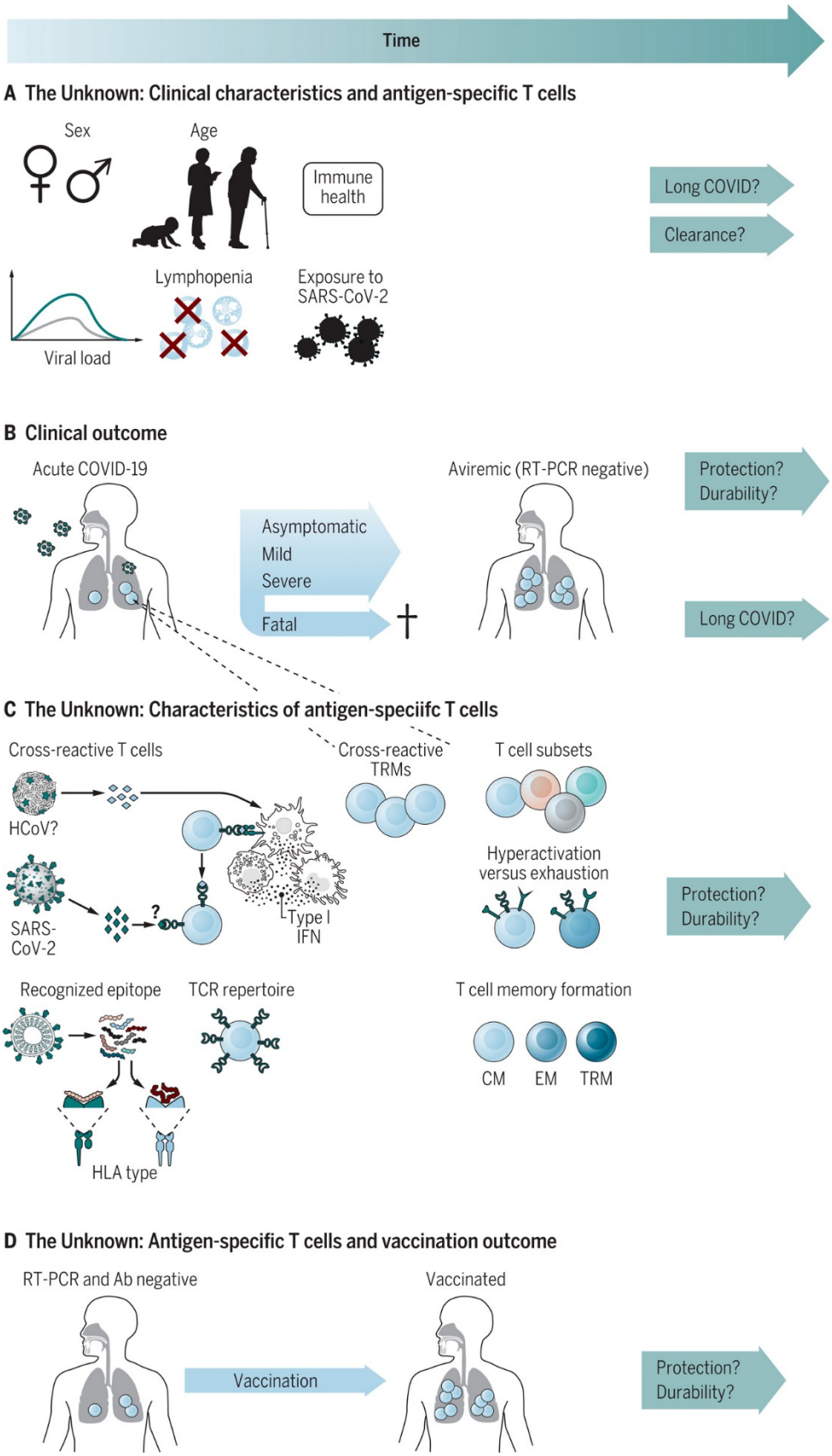

Fig. 1. The unknowns about T cells in COVID-19 in relation to disease severity, memory formation and vaccination. (A) Clinical and virological factors likely to be related to the development and function of antigen-specific T cell responses against SARS-CoV-2. The impact of factors including sex, age, chronic conditions affecting immune health, viral load dynamics, degree of lymphopenia, and risk of exposure to SARS-CoV-2, on the strength and efficacy of the early antiviral T cell response remains elusive. Furthermore, some individuals experience delayed viral clearance or other symptoms for an extended period (long COVID) despite viral clearance. (B) The broad clinical spectrum of acute COVID-19 includes asymptomatic, mild, severe, and fatal outcomes. Whether convalescent individuals will be protected against SARS-CoV-2 (re)infection and the longevity of this protection remain to be determined. (C) Immunological and virological factors influence generation of SARS-CoV-2-specific T cells and may influence the clinical manifestations and quality of the induced T cell response in acute and convalescent COVID-19 patients. Here, the ability of the host to generate efficient T cell responses following SARS-CoV-2 infection are likely to be dependent on the epitopes targeted, antigen abundance, involvement of resident memory T cells (T_{RM}) at the site of infection, presence or absence of preexisting cross-reactive T cells, and host genetic factors such as HLA type and TCR repertoire. Furthermore, the level of inflammation and amount of proinflammatory cytokines are likely to be associated with T cell activation and exhaustion and subsequent T cell memory formation. (D) The potential link between vaccination outcome in relation to T cell immunity remains to be determined. CREDIT: A. KITTERMAN/*SCIENCE IMMUNOLOGY*

Box 1. Open questions about T cell immunity to SARS-CoV-2.

T cells in acute SARS-CoV-2 infection

- What do acute SARS-CoV-2-specific T cell responses in the blood tell us about contemporaneous T cell responses in the lung?
- Which host and viral factors regulate the strength and efficacy of the early antiviral T cell response?

Longevity and memory T cell formation

- Do $CD4^+$ T cell responses to the virus predominate over $CD8^+$ responses in the lung as well as the blood?
- Do poor $CD4^+$ T_{FH} responses to the virus correlate with reduced longevity of antibody responses?
- Is severe COVID 19 linked to an impaired development of SARS-CoV-2-specific memory T cells?

Cross-reactive T cells

- Do pre-existing memory T cells to seasonal CoV epitopes help or hinder the host response to SARS-CoV-2?

SARS-CoV-2-specific T_{RM}

- Will establishment of SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T_{RM} in the upper respiratory tract provide durable protection from lower pulmonary disease upon reinfection?

Long COVID

- Are virus-induced or bystander T cells major inducers of persistent symptoms of inflammation associated with long COVID?

T cells in vaccines

- What type of T cell response elicited by vaccines will be the best predictor of protection from disease following exposure to the virus?

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The known unknowns of T cell immunity to COVID-19

Annika C. Karlsson, Marion Humbert and Marcus Buggert

Sci. Immunol. **5**, eabe8063.
DOI: 10.1126/sciimmunol.abe8063

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