

INSIGHTS

Lasting memories of SARS-CoV-2 infection

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Maintaining virus-specific adaptive immunity is critical for ongoing protection against SARS-CoV-2 infection. In this issue, Breton et al. (2021. *J. Exp. Med.* <https://doi.org/10.1084/jem.20202515>) identify polyfunctional SARS-CoV-2-specific T cell responses in the peripheral blood of individuals who recovered from COVID-19 that were present at 1 mo and persisted until 6 mo after infection.

In the midst of the devastating COVID-19 pandemic, the scientific community has come together in an unprecedented global effort to understand the immune responses to SARS-CoV-2 infection in order to develop effective strategies for treatment and prevention of disease. In particular, studies in mouse infection models and extensive analysis of human samples from acutely infected and convalescent individuals have shown that SARS-CoV-2-specific adaptive immune responses play a prominent role in antiviral protection. The generation of neutralizing IgG antibodies directed against the Spike (S) protein on the virus surface, which binds the cellular receptor for viral entry, can block infectivity, provide protection in an animal model, and be used therapeutically (Hansen et al., 2020; Rogers et al., 2020; Hassan et al., 2020). Meanwhile, studies of convalescent patients have shown that SARS-CoV-2-specific T cells are reactive against multiple viral proteins; the most predominant and robust are S-protein-specific CD4⁺ T cells, which further correlate with antibody responses (Grifoni et al., 2020; Rydzynski Moderbacher et al., 2020). As we move toward optimizing vaccine strategies to protect the global population and end the pandemic, it is important to define the durability and longevity of virus-specific immunological memory to primary SARS-CoV-2 infection.

In this issue of *JEM*, Breton et al. (2021) investigated the persistence of cellular immunity to SARS-CoV-2 infection in previously infected individuals at two distinct time points—1 and 6 mo after infection—compared with healthy controls (Breton et al., 2021). The authors examined the maintenance and functional capacity of virus-specific T cells by stimulating peripheral blood CD4⁺ and CD8⁺ T cells with SARS-CoV-2 peptide pools corresponding to surface structural proteins—S and membrane protein (Memb)—and internal virion proteins—nucleocapsid (NCAP) and protein 3a (AP3a). The functional readout was assessed by secretion of cytokines (IL-2, IFN- γ , TNF- α , MIP-1 β) and expression of activation/cytotoxicity markers (CD154, CD107a). They showed that while both CD4⁺ and CD8⁺ virus-specific T cells are broadly reactive against all four SARS-CoV-2 epitopes tested, the magnitude of the CD4⁺ T cell response was much greater, while CD8⁺ T cell responses were more variable and less robust (see panel A of figure). These results are consistent with earlier studies showing that CD4⁺ T cell responses induced by natural infection are more robust than CD8⁺ T cell responses (Grifoni et al., 2020). Moreover, Breton et al. (2021) showed correlation between CD4⁺ and CD8⁺ T cell responses specific for Memb, NCAP, and AP3a, although S-specific T cell responses were predominantly CD4⁺ and did not correlate



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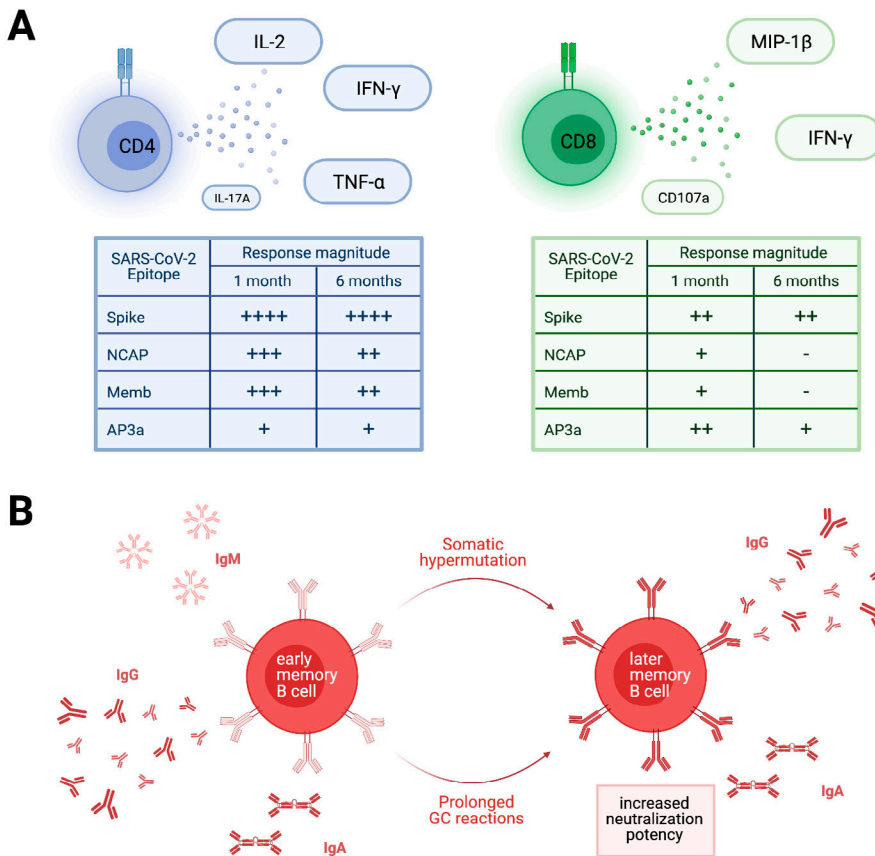
with the corresponding CD8⁺ T cell response. SARS-CoV-2-specific CD4⁺ T cells exhibited an effector-memory phenotype.

CD4⁺ SARS-CoV-2-specific T cells exhibited polyfunctionality in the ability of individual T cells to produce multiple cytokines such as IL-2, IFN- γ , and TNF- α upon recall. Polyfunctional S-specific memory CD4⁺ T cells were comparably present at both 1 and 6 mo after infection; however, the polyfunctional responses of NCAP- and Memb-specific CD4⁺ T cells were reduced at the 6-mo compared with 1-mo time point. For CD8⁺ T cells, MIP-1 β was consistently produced in response to the different SARS-CoV-2 epitopes and was maintained across time points in recovered individuals compared with healthy controls. This important study is joined by recent findings also demonstrating longevity of SARS-CoV-2-specific CD4⁺ T cells 3–8 mo after infection

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Maintenance and evolution of adaptive immunity to SARS-CoV-2 infection. (A) T cell-mediated immunity consists of SARS-CoV-2-specific CD4⁺ and CD8⁺ T cells that produce cytokines upon stimulation and are reactive against a broad range of viral epitopes. Charts show relative responses to different viral epitopes (S, Memb, NCAP, AP3a) 1 and 6 mo after infection. CD4⁺ T cell responses specific for the S protein predominate and are maintained long-term, while T cells specific for other viral epitopes are reduced at 6 mo after infection; CD4⁺ T cell responses are more robust than CD8⁺ T cell responses. (B) Humoral immunity to SARS-CoV-2 is maintained by circulating antibodies, particularly IgG and IgA, and memory B cells. Memory B cells undergo somatic hypermutation and prolonged germinal center reactions after the resolution of natural infection, resulting in increased neutralization potency over time.

(Dan et al., 2021; Rodda et al., 2021). Together, these T cell analyses show that persistent cellular immune memory, particularly CD4⁺ T cell memory, is maintained after COVID-19 and possesses the capacity to elicit a robust response upon reexposure to SARS-CoV-2.

The longevity of humoral immunity and memory B cells has also been examined by this group using the same cohort at 1 and 6 mo after infection (Gaebler et al., 2021), as well as several other studies (Dan et al., 2021; Rodda et al., 2021). They found that IgM, IgG, and IgA can be detected in circulation up to 8 mo after infection, with IgM titers decreasing rapidly over time and IgG and IgA titers remaining more stable (see panel B of figure; Dan et al., 2021; Rodda et al., 2021; Gaebler et al., 2021). These

studies also confirmed the persistence of neutralizing antibodies, which appear to decrease but remain detectable at 6 mo after infection. Interestingly, the frequencies of circulating memory B cells increased between 1 and 6 mo after infection (Dan et al., 2021; Gaebler et al., 2021). Gaebler et al. (2021) demonstrated that the maintenance of humoral immunity to SARS-CoV-2 is dynamic and evolves over time. Sequencing of SARS-CoV-2-specific paired antibody heavy and light chains from individuals at 1 and 6 mo after infection revealed a significant increase in somatic hypermutation at 6 mo compared with earlier samples, consistent with ongoing evolution of the antibody response (panel B of figure). In addition, when comparing antibodies present at both time points, antibodies at 6 mo

exhibited increased neutralization potency (panel B of figure). Together, these studies indicate that the humoral response not only persists following SARS-CoV-2 infection, but also further adapts to provide enhanced protection against secondary exposure, perhaps by prolonged germinal center reactions mediated by antigen persistence in tissues (panel B of figure). This elevation in the frequency and potential affinity of the memory B cell response may compensate for any diminishment in T cell responses that occur over time.

The studies by Breton et al. (2021) and others show promising results that highlight the maintenance of SARS-CoV-2-specific immune cells and antibodies following natural infection. It would be interesting to assess how these circulating T and B memory cells correlate to their presence in tissues. Studies in mouse models have shown that lung tissue-resident memory T cells provide enhanced protection, compared to circulating T cells, against secondary respiratory virus infection (Tejaro et al., 2011). Furthermore, studies from paired respiratory wash and blood samples in severe COVID-19 show activated tissue-resident memory T cells in the airways that do not correlate to T cell responses in blood (Szabo et al., 2021). As the presence of SARS-CoV-2-specific CD8⁺ T cells in blood is low and variable, it is not yet clear how or whether circulating virus-specific T cell responses reflect those required to clear virus and limit spread in the respiratory tract. Similarly, memory B cells in humans are not abundant in circulation and are present in much greater frequencies in lymphoid tissue (Weisel et al., 2020). In order to fully assess the lasting immune protection induced by SARS-CoV-2 infection, studies examining virus-specific immunity within tissue sites of infection would be informative.

As global efforts move forward with development and distribution of vaccines to finally put an end to the COVID-19 pandemic, results from these studies also provide valuable insight into the enduring protection established against viral proteins. Importantly, findings from Breton et al. (2021) and others demonstrate immunodominance of the response to the S protein that persists and further adapts for many months after the initial infectious challenge. These results augur well for long-term durability of protection mediated by

S-protein-containing vaccines, which have shown impressive efficacy in early trials (Polack et al., 2020; Baden et al., 2021). These current vaccines may further boost S-specific T and B cell memory responses and enhance existing immunity to primary SARS-CoV-2 infection. Together, widespread vaccination of individuals—either naive or those primed from previous infection—will generate diverse types of immune reactants to clear an infection, thus preventing dissemination of infection within the body and reducing viral load. In this way, the adaptive immune system

creates a fortified defense system to end this current pandemic and mitigate the impact of future ones.

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