

Primer

T Cell Memory: Understanding COVID-19

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As the SARS-CoV-2 pandemic has progressed, increasing attention has focused on establishing natural and vaccine-induced immunity against this coronavirus and the disease, COVID-19, that it causes. In this Primer, we explain the fundamental features of T cell memory and their potential relevance for effective immunity to SARS-CoV-2.

Basic Concepts in T Cell Memory

T cells are important regulators of cellular and antibody-mediated (humoral) immunity. Conventional T cells, distinguished by the expression of the cell-surface receptors CD4 and CD8, use clonally variable T cell receptors (TCRs) to recognize antigens derived from pathogen proteins in the form of peptide fragments associated with major histocompatibility complex (MHC) molecules (human leukocyte antigen [HLA] in people). This leads to T cell differentiation into a range of effector cell types tailored to control the invading organism (Table 1). Different types of pathogens require distinct immune effector cell types to be controlled. In the case of viral infections, these usually include “follicular helper” CD4⁺ T (Tfh) cells that induce B cells to produce high-affinity antibodies capable of neutralizing the pathogen and cytolytic CD8⁺ T cells that kill pathogen-infected cells. Clonal diversity in the pre-immune “naive” T cell population means rare cells will be present with TCRs able to recognize a new pathogen, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In a productive immune response, these specific T cell populations undergo dramatic numerical increases and differentiate to manifest appropriate effector functions for elimination of the pathogen. This is usually followed by a substantial loss of effector cells but preservation of an elevated number of durable “memory” T cells of various types, also termed subsets (Table 1), which can be efficiently deployed if an individual is reinfected by the same pathogen (Figure 1A). Since effective immune memory can persist for decades and typically results in enhanced responses and accelerated pathogen control, generation of robust and durable T and B cell memory is a goal of vaccines, including the many vaccines against SARS-CoV-2 that are currently in human trials.

Memory T cells, whether generated by natural infection or deliberate vaccination, differ from their naive counterparts in several ways that are evident during recall responses—when the organism encounters the pathogen for a second time. Collectively, these features result in recall responses that are quantitatively and qualitatively different than the primary responses made by naive T cells. Hallmarks of memory T cell responses include (1) an increased pool of memory T cells reactive to the pathogen through specific recognition of pathogen-derived antigens by the TCR, (2) a more rapid and powerful response to infection, (3) preprogramming to generate a “tailored” set of effector cell types optimized to fight the pathogen, which includes recall Tfh responses to help boost humoral immunity, and (4) the

presence of memory T cells in barrier tissues as a means of rapid detection and control of infection. This last hallmark is dominated by resident memory T cells (Trm) that are maintained in non-lymphoid tissues, including the lung, and do not exchange with populations in the circulation: a practical consequence, being that this important population is not represented in blood, the most commonly monitored tissue in humans, complicating the assessment of Trm generation and persistence.

In order to develop memory T cells capable of mediating a robust recall response, the primary response must effectively and safely clear the pathogen to allow the differentiation of memory T cell progenitors into fully formed memory populations. A prerequisite is a pool of high-affinity naive T cells recognizing pathogen-derived peptides to generate a robust response. As individuals age, the naive T cell pool declines due to decreased T cell output from the thymus as well as loss of naive T cells over time through activation or attrition, which could compromise the response of elderly individuals to a novel pathogen. Assuming a high-quality pool of naive T cells is available, these cells must also receive the proper signals during activation to mount a successful effector response to control the infection while also producing memory progenitor cells to deal with potential future reinfections. These signals include soluble factors, such as cytokines and cell-cell interactions, including with dendritic cells presenting pathogen-derived antigens and costimulatory (or inhibitory) ligands to naive T cells, as well as CD4⁺ T cell help to CD8⁺ T cells. If any of these requirements are not met appropriately, the primary response may be ineffective or overblown, resulting in pathology in the host and/or impaired development of memory. In the case of ineffective priming or generation of “exhausted” T cells that progressively lose effector potential due to an unresolved, chronic infection (Figure 1B), these T cell populations are likely to either be lost over time or enter a permanently dysfunctional state, even if the host survives. At the other extreme, T cell responses may become dangerously exuberant, leading to excessive tissue damage and/or a life-threatening cytokine storm, collectively termed immunopathology (Figure 1C). This can lead to persistent, systemic changes in the immune system altering future immune responses, including the development of memory cells and their response to rechallenge with the offending pathogen. One final possibility we will consider is that an individual’s microbial experience may mean they don’t start with an immunologically “clean

Table 1. Title

T Cell			
Subset/ Trait	CD4/ CD8	Location	Function
Effector	both	bodywide	termination of infection
Type 1	both	sites of infection	response to intracellular pathogens
Type 2	mostly CD4	sites of infection	response to large extracellular parasites
Type 17	mostly CD4	sites of infection	response to extracellular bacteria and fungi
Tfh	CD4	lymphoid tissues	promotion of B cell response
Treg	CD4	bodywide	tolerance/control of immunopathology
Cytotoxic	mostly CD8	sites of infection	killing of infected cells
Memory	both	bodywide	preservation of antigen-specific immunity tailored to pathogens for rapid future responses
Central/ stem cell	both	lymphoid tissues, circulation	long-term maintenance of circulating memory
Effector	both	circulation, peripheral tissues	periodic patrol of non-lymphoid tissues
Resident	both	tissues	very rapid response at site of reinfection
[Exhausted]	both	distinct stages in diff. sites	impaired function/avoidance of immunopathology

slate”—for example, memory T cells generated in response to one pathogen may cross-react with another with highly similar antigens, such that the response to a “new” pathogen involves reactivation of pre-existing memory T cells (Figure 2) and thus differs from the other scenarios. This can result in a variety of outcomes, including enhanced control as compared to a *de novo* naive response, as will be discussed further. There is emerging evidence that all these modes of memory T cell generation and response may occur among patients experiencing natural SARS-CoV-2 infection, with possible implications for natural immunity and the efficacy of vaccines currently under development to contain coronavirus disease 2019 (COVID-19).

Generating Effective T Cell Memory and Why It Matters

A protective primary T cell response against a viral pathogen requires recruitment and activation of antigen-specific naive CD4⁺ and CD8⁺ T cells, rapid population expansion, and differentiation into suitable effector cell types to mediate an appropriate immune response. In the case of SARS-CoV-2, CD4⁺ and CD8⁺ T cells producing interferon (IFN)- γ (commonly referred to as a “type 1” immune response), CD4⁺ Tfh cells promoting potent virus-neutralizing antibody generation by B cells, and cytolytic CD8⁺ T cells capable of killing infected cells are expected to be protective. Diversion of CD4⁺ T cells to produce type 2, type 17, or inhibitory populations (T regulatory cells) and generation of exhausted CD8⁺ T cells may impede viral control (although minor contributions by these alternative responses

may be beneficial to contain immunopathology). T and B cell responses during COVID-19 have been tracked in blood samples, allowing identification of SARS-CoV-2-specific type 1 CD4⁺ and CD8⁺ T cell responses and the presence of SARS-CoV-2-specific neutralizing antibodies in COVID-19 patients and vaccine recipients. Similar data are emerging to indicate that SARS-CoV-2-specific memory T cells are produced—with the major caveat that less than a year has elapsed since the virus was first detected in the human population, a relatively short time frame in terms of human immunological memory, which can persist for decades (for example, the half-life of memory T cells specific for the smallpox vaccine is on the order of 8–15 years). However, it is unclear how well analysis of blood reflects the status of functional T cell memory. For example, Tfh memory cells in lymphoid tissues can efficiently produce Tfh cells during secondary immune responses and hence are likely poised to support recall T-dependent B cell responses, but whether the frequency and function of this population is faithfully represented by circulating memory Tfh cells is less clear. Furthermore, CD4⁺ and CD8⁺ Trm cannot, by definition, be assessed in blood samples, yet these cells may be critical as frontline responders, capable of containing reinfection with the same pathogen at the point of entry. Therefore, clinical blood samples may not permit comprehensive assessments of functionally relevant T cell memory in people who have recovered from SARS-CoV-2 infection or been vaccinated. Ways to promote generation of particular memory T cell subsets following deliberate vaccination are starting to be explored—for example, the generation of Trm in desired tissues can be enhanced by leveraging cytokine and chemokine cues following immunization, and altering the route of vaccination can substantially affect the generation of protective T cell memory. It is currently unclear whether such manipulations would improve the potency of SARS-CoV-2 vaccines.

But why should we care about T cell memory in the context of the SARS-CoV-2 pandemic? Current studies on the response to natural SARS-CoV-2 infection and to candidate vaccines are, appropriately, focused on generation of high-affinity neutralizing antibodies as a key endpoint. Once generated, long-lived plasma cells have the potential to produce antibodies for decades in the apparent absence of re-encounter with antigen or specific T cells. Passive transfer of neutralizing antibodies to decrease viral load is a promising therapeutic approach currently in clinical trials. In light of antibody responses, whether T cell memory is actually important for durable protective immunity against SARS-CoV-2 is a legitimate question.

However, two scenarios reinforce the relevance of effective T cell memory. First, inadequate generation or persistence of neutralizing antibodies could limit the efficacy and longevity of serological immunity against SARS-CoV-2 infection or vaccination. This is not just a hypothetical concern—long-term studies of patients who recovered from the closely related SARS (now also called SARS-CoV-1) virus in 2002–2004 indicated that anti-SARS T cells were long lived and remained nearly two decades later, while anti-SARS circulating memory B cells and antibodies were below the limit of detection in most individuals. Patients recovering from SARS-CoV-2 display stable serum antibodies for several months, but there is emerging evidence that severe COVID-19 may compromise the generation of potent, long-lived

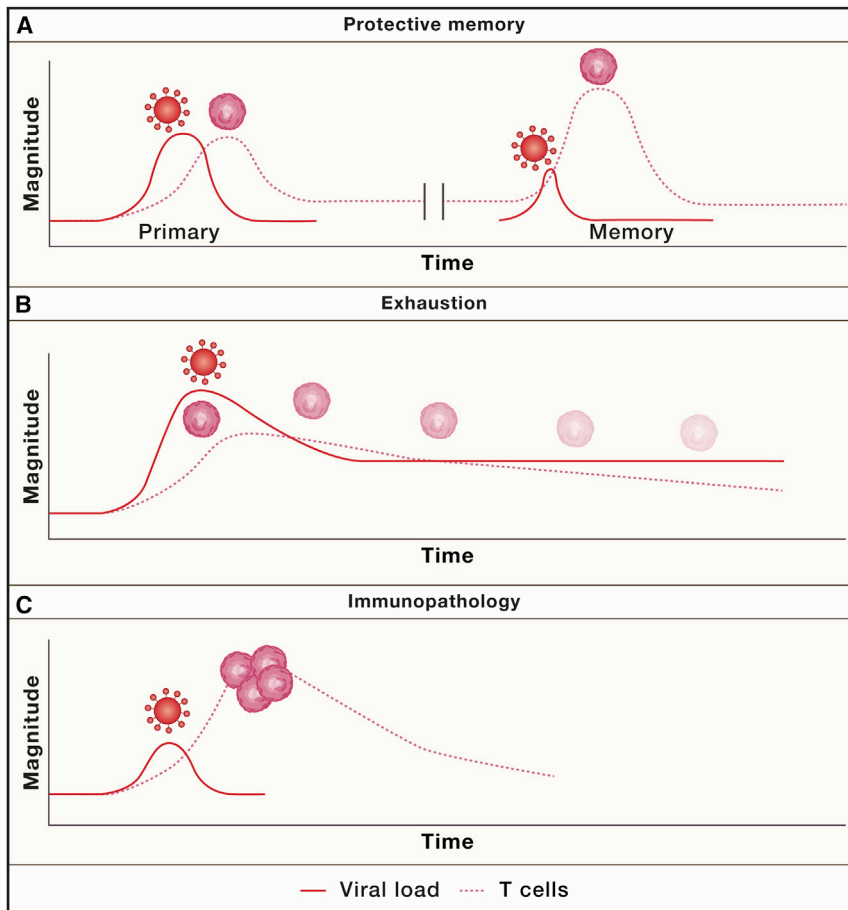


Figure 1. Outcomes of Primary Immune Responses and Effects on Memory Development

(A) In the ideal scenario, when a pathogen (red virus) infects an organism and begins to replicate to high levels, an appropriate T cell response specific to that pathogen (pink T cells) develops and contributes to control and clearance of the infectious agent. The T cell population is then maintained at a low frequency as a mixture of memory subsets (Table 1). B cell memory (not shown) is also generated. If the same pathogen later reinfects the individual, memory T cells will rapidly respond and contribute to clearing the pathogen more quickly than during the primary response. However, there are also several less-optimal outcomes.

(B) If the immune response cannot clear the infectious agent, a chronic infection will develop. This can cause T cells to enter a so-called exhausted (or hypofunctional) state (represented by lighter-colored T cells) rather than developing classical memory.

(C) If the initial response is too strong (represented by dark red T cells), the immune response can cause damaging immunopathology, potentially including a cytokine storm. This can be fatal, and survivors may have lasting changes in subsequent immunity (not shown).

this diversity broadens the opportunity for immune recognition beyond the proteins displayed on the viral envelope (the targets for neutralizing antibodies), providing a platform for enhanced and accelerated generation of new B cell responses against viral variants and strains while also providing direct responses (e.g., inflammatory cytokine responses

antibody responses while T cell memory is established in symptomatic and asymptomatic subjects. At a minimum, T cells may provide a second arrow in the quiver of immunological memory—for example, Trm could detect reinfection and coordinate recall responses in barrier tissues, and Tfh cells could boost the B cell response, generating higher levels of higher-affinity protective antibodies.

In the second scenario, regardless of the potency of the initial SARS-CoV-2 response, mutations in the virus or emergence of distinct but related SARS-CoV-2 strains could limit the efficacy of neutralizing antibodies. Coronaviruses including SARS-CoV-2 undergo a lower mutation rate than many RNA viruses because they encode a proofreading enzyme to correct genome replication errors, but because of the wide spread of SARS-CoV-2, there are nonetheless numerous variants present. None of these are currently known to affect neutralizing antibody binding to the spike (S protein), but neutralizing antibodies will provide an increasingly potent selective pressure for viral escape mutants as population immunity increases via natural infection and vaccines. Many COVID-19 patients display a robust CD4⁺ and CD8⁺ T cell response toward diverse SARS-CoV-2 viral proteins, including S, membrane (M), nucleocapsid (N), nonstructural proteins (NSPs), and orphan reading frames that are detectable for at least several weeks after symptom onset. Assuming memory T cells develop from these,

and cytolysis) to effectively hold back the infection as these new responses develop. It's also worth noting that we have only a hazy idea of the “correlates of protection” against SARS-CoV-2—i.e., in this case, what elements of the adaptive immune system provide functional immunity: while neutralizing antibodies are thought to be critical, other elements, including T cell memory, are likely beneficial. Furthermore, while it is hoped that protective immunity against SARS-CoV-2 will block initial infection, thereby eliminating both symptomatic disease and viral shedding, it is also possible that memory responses against SARS-CoV-2 could either ameliorate symptomatic disease or limit viral shedding, but not both. For example, a robust Trm response in the lung could limit infection, potentially reducing clinical symptoms by averting a full, systemic immune response while still allowing viral shedding for a period, perhaps from other mucosal surfaces (such as the nasal passage). This scenario could have detrimental effects in a largely SARS-CoV-2-naive population by contributing to viral shedding by individuals not showing symptoms. On the other hand, a too-robust local and systemic response to SARS-CoV-2 reinfection could quickly eliminate the virus but result in immunopathology. While we strongly believe that immune memory responses after natural SARS-CoV-2 infection or vaccination will be beneficial, these examples illustrate the importance of working out the correlates and benefits of immune protection.

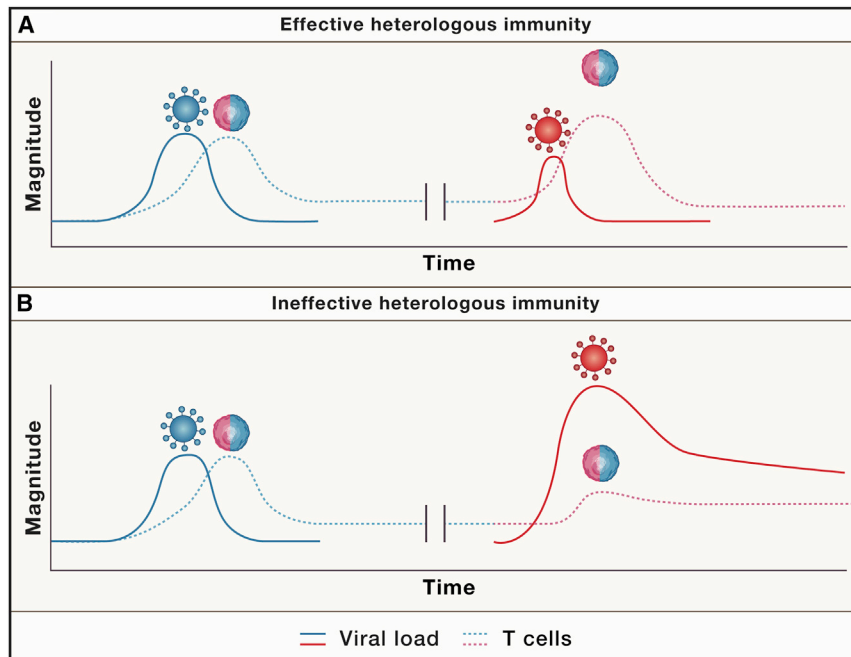


Figure 2. Heterologous Immunity to Viruses

Responses to one pathogen (blue virus) may produce memory T cells that cross-react with antigens from a different pathogen (red virus) (heterologous immunity). Several outcomes are possible.

(A) If cross-reactive T cells mediate a rapid and effective immune response, this results in a memory-like heterologous immune response to the red virus, mediating enhanced control compared to a *de novo* primary response.

(B) In contrast, cross-reactive T cells may be incapable of mediating an effective immune response to the red virus, instead causing immunopathology (not shown) and/or suppressing the *de novo* primary response to that pathogen by outcompeting antigen-specific naive T cells. In this case, heterologous immunity may cause more tissue damage and/or impaired control of the infection than a *de novo* primary immune response.

The Significance of Pre-existing T Cell Memory to SARS-CoV-2

While our discussion has so far focused on T cell memory as a result of SARS-CoV-2 infection or vaccination, several groups have detected CD4⁺ and CD8⁺ T cells (but not antibodies) reactive to SARS-CoV-2 proteins in SARS-CoV-2-naive individuals—for example, in blood samples banked years before the current pandemic. Some of these likely are cross-reactive memory T cells that arose from prior infections with other coronaviruses. This has led to much speculation as to whether these seemingly cross-reactive memory T cells are beneficial, pathological, or irrelevant in the event of SARS-CoV-2 infection. Despite the exquisite specificity of T cell responses, their recognition of short peptides means that cross-reactivity between distinct pathogens is not uncommon, resulting in so-called heterologous immunity. As discussed earlier, pre-existing T cell memory could foster more rapid responses to SARS-CoV-2 infection or vaccination and enhance generation of neutralizing antibodies, benefitting individuals carrying such cross-reactive cells (Figure 2A). While we consider this the most likely association, it is worth noting that there are instances in which heterologous memory responses are ineffective or have negative consequences, including impaired pathogen control and/or immunopathology (Figure 2B). T cell responses generally focus on a select few peptides from a given pathogen, a property termed “immunodominance,” which can be dramatically altered by the presence of heterologous T cell memory. It has been described that the dominant targets of the pre-existing SARS-CoV-2-reactive T cells observed in some healthy individuals are different than those induced in COVID-19 patients, with healthy donors exhibiting significant reactivity with S and NSP peptides but a lower frequency of responses to the N and M proteins as compared to COVID-19 patients. Whether this altered balance influences

the response to SARS-CoV-2 infection and/or vaccination in subjects with such pre-existing memory T cells is not known, nor are any positive or negative consequences for control of the pathogen or generation of neutralizing antibodies. As a high proportion of the world’s population will presumably become infected with SARS-CoV-2 or be vaccinated, whether either of these events will alter our responses to other coronaviruses in the future should also be carefully monitored. Hence, the significance of memory T cell cross-reactivity between SARS-CoV-2 and other coronaviruses is unclear but will undoubtedly be the topic of considerable investigation.

How Variation in Responses to SARS-CoV-2 Could Impact T Cell Memory

In the human population, the course of COVID-19 disease varies dramatically, ranging from asymptomatic and/or mild infection to life-threatening illness. Early in the pandemic, it became apparent that advanced age is a significant risk factor for severe disease. These aspects of COVID-19 raise concern as to whether the development of immune memory varies depending on the age of the individual or the severity of disease. As discussed earlier, the naive T cell pool becomes smaller in older individuals, which could conceivably impair responses to novel pathogens, as has been proposed for SARS-CoV-2. However, it is still unclear whether T cell memory against SARS-CoV-2 is broadly impaired in the elderly after natural infection or vaccination. As successful vaccination of older individuals is particularly challenging, whether the vaccine candidates currently in development can induce protective immunity, including T cell memory, in the elderly will greatly influence the effectiveness of targeted vaccination of high-risk groups.

The development of T cell memory is intimately tied to the dynamics of the immune response. For classical memory to develop, the infectious agent (or at least its protein antigens) must be cleared. When this does not take place during chronic infections (such as HIV), responding T cells may become exhausted as a result of specific cytokine signals and continual TCR stimulation.

It has been suggested that some COVID-19 patients may develop exhausted T cell populations, mostly based on a limited set of surface markers or transcriptome analysis. SARS-CoV-2 is thought to be an acute pathogen, but COVID-19 patients can experience weeks of exacerbated inflammation that could conceivably alter T cell function. However, severe COVID-19 does not appear to eliminate T cell responses, as assessed weeks after symptom onset, and care must be taken with measurements made early after infection, since some “exhaustion” markers are expressed on recently activated T cells. Whether SARS-CoV-2 causes T cell exhaustion and/or impaired T cell memory generation in a subset of patients remains to be determined. Other recent studies assessing a combination of infectious and recovered COVID-19 patients indicated that those with mild disease developed detectable T cell immunity, though possibly with some altered characteristics compared to the responses in severe COVID-19 cases. While a proportion of patients with severe COVID-19 have severe defects in the T cell response, it is unclear whether defects in the T cell response contribute to or are a consequence of progression to severe COVID-19, and the impact on eventual generation of T cell memory in survivors will be important to assess. To this point, T cell immunity at early time points after COVID-19 generally appears to be relatively resilient across a spectrum of disease severity. As SARS elicits more severe disease and more durable memory than common cold coronaviruses, whether more severe COVID-19 disease will result in more durable T cell memory is a relevant and important question to address.

Recap

Even in the midst of an active infection, the immune system makes an investment in the future of the host by selecting activated T cells to become memory progenitors. If the primary response successfully wards off the infection, the organism will in most cases go on to preserve part of that immune response in the form of memory T cells. Because of the successful resolution of the prior infection, these memory T cells are a known quantity and are thus preserved at an increased frequency throughout the body, ready to mediate an enhanced and accelerated response to reinfection. But T cell memory is not just important as a source of new effector T cells—memory T_{fh} responses can enhance memory B cell responses upon rechallenge, which becomes particularly important in the context of pathogen evolution to evade antibody recognition. For these reasons, a major goal of all new vaccines (including those against SARS-CoV-2) should be to elicit T cell memory in both the circulation and tissues. In the contexts of both natural SARS-CoV-2 infection and vaccination, it will be crucial to track stability of circulating and tissue-resident T cell memory over months and years in humans and animal models. Although work on SARS suggests that T cell memory to SARS-CoV-2 is likely long lived, further research and simply more time is required for full assessment of the duration of immunity to SARS-CoV-2. Furthermore, whether pre-existing SARS-CoV-2-reactive T cells in naive individuals provide beneficial immunity, promote an ineffective response by biasing the responding population, or cause immunopathology remains unanswered, but it is likely that these

populations will have a role in the development of anti-SARS-CoV-2 memory responses.

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