Lessons in antiviral immunity

Immune responses to SARS-CoV-2 reveal regulation and dynamics of lymphocytes

By Jennifer L. Hope and Linda M. Bradley

The adaptive branch of the immune system can kill virally infected cells and generate protective immune memory, which is the basis of vaccination strategies. Both T cell and B cell responses are important in controlling viruses and the development of immunity. However, the COVID-19 pandemic is revealing widely varying immune responses and diverse clinical outcomes with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, raising questions about how antiviral responses are orchestrated, factors that influence the longevity of immunological memory, and approaches that mediate robust protection from viral infections.

Viruses are responsible for many diseases, with effects on human health ranging from mild infections to those that are potentially fatal. Viruses infect host cells and then take over the cellular machinery to replicate and spread to susceptible cells. Viral infections, which can be localized or systemic, elicit innate immune responses (such as inflammation) that in turn activate the adaptive immune system. Viral proteins and particles are taken up by dendritic cells (DCs) that transport them into lymphoid organs, where they are specifically recognized by T and B cells. Ultimately, the cellular (T) cell and humoral (B) cell branches of adaptive immunity work together to enable highly specific defenses against diverse viruses with the following general features.

T cell recognition of viral peptides and B cell recognition of viral proteins both begin in lymphoid tissues, where DCs present peptides to T cells, and B cells sample viral proteins, together initiating the development of effector cells to eliminate the virus. The magnitudes of the T and B cell responses are determined by such factors as the pathogenicity of the virus, the extent of inflammation, the frequencies of virus-specific T and B cells, and the kinetics of viral replication. CD8+ T cells differentiate into effector cells that limit viral replication through production of cytokines and direct killing of infected cells. For CD4+ T cells, viral recognition elicits cytokine-producing effector cells, such as T helper 1 (T(H)1) cells, which inhibit viral replication and support CD8+ T cell as well as B cell differentiation. Effector T cells can enter the circulation and relocate to tissue sites of infection, where they mediate local antiviral responses. CD4+ T cells also differentiate into T follicular helper (T FH ) cells that are crucial for the development of antibody-producing B cells (plasma cells) in lymphoid tissues and support memory B cell development. Antibodies can neutralize viruses by preventing host cell entry or promoting the lysis of infected cells. As a result of the coordinated interplay of innate and adaptive responses, the peak T and B cell responses lead to decreasing viral load (see the figure) and subsiding inflammation, often within 1 week of infection.

After viral clearance, the majority of effector T and B cells contract and die. Small pools of resting memory T cells form while persisting B cells generate either long-lived antibody-producing plasma cells or resting memory B cells. These heterogeneous memory cell populations are capable of rapid responses upon reinfection. Virus-specific T cells responding when viral titers are high can retain effector properties as memory cells (effector memory cells), whereas those responding as a viral infection becomes contained typically generate memory cells with a capacity for self-renewal (central memory cells) that serve as a reservoir for protection during future reinfections. T cells located in sites of infection can become specialized tissue-resident memory (T TRM ) cells. However, when adaptive immune responses to infection are suboptimal or a virus has evolved means to evade immune responses (including the induction of host immune suppression), chronic infection or widespread illness and death can ensue, especially in at-risk individuals. SARS-CoV-2 infection demonstrates varied disease severity and highlights the need for greater understanding of the factors that determine effective adaptive immune responses and long-lasting protective immunity, particularly in vulnerable populations, such as older people or immunocompromised individuals.

A key factor in eliminating virus infections is whether robust, high-affinity T and B cell antiviral responses are elicited. Naive T and B cell pools demonstrate a wide range of viral recognition due to the highly diverse T cell receptor (TCR) and B cell receptor (BCR) repertoires established during cellular development. Clones with high-affinity TCRs are selected during infection because of their greater ability to bind viral peptides. By contrast, BCR affinity continues to increase for viral proteins over the course of infection through the processes of somatic hypermutation and clonal expansion. Additionally, B cells undergo antibody class switching from early immunoglobulin M (IgM) production to higher-affinity IgG and IgA subtypes, which have specialized immune functions and are all detected in the sera of convalescent COVID-19 patients. The magnitude of early antibody responses may be indicative of the severity of infection, because higher IgM and IgG antibody titers are associated with more severe disease (1). Similar to other viral infections, the overall serum titers of SARS-CoV-2–specific antibodies wane following clearance of the active infection. However, long-lived memory B cells can remain and produce circulating, virus-neutralizing antibodies. A recent study showed that 6 to 8 months after COVID-19 disease onset, SARS-CoV-2–neutralizing antibodies were found in 90% of recovered patients (2). It is also important to track and compare the duration of memory B cell responses from natural SARS-CoV-2 infection and from vaccines.

Adaptive immune responses to viruses can also be influenced by the history of previous virus encounters. For example, T RM cells residing in the lungs can recognize conserved internal structural proteins of influenza viruses and subsequently can reduce the severity of infection by new strains of influenza virus (3). T cells reactive to SARS-CoV-2 proteins have been detected in individuals previously infected with SARS-CoV and in nonexposed healthy individuals (4, 5). These findings indicate that memory T cells are generated by infections with other human coronaviruses (HCoVs), including “common cold” coronaviruses. Similarly, IgG antibodies from COVID-19 patients were found to strongly react to proteins conserved among common cold HCoVs. Conversely, SARS-CoV-2–reactive antibodies specific for conserved HCoV proteins were detected in sera from people who had not had COVID-19 (6); these may be broadly neutralizing antibodies. It is not yet clear whether these preexisting SARS-CoV-2–reactive T and B cells can contribute to better disease outcomes. If they can, their high reactivity suggests that it may be desirable to expand such T and B cell populations through vaccination.

The extent of infection and inflammation engendered by viruses, including SARS-CoV-2, is important because excessive in-
Adaptive immune responses to viral infections

Adaptive immune responses control and eliminate viral infections that have outpaced innate immune control. Days after infection, virus-specific cytotoxic CD8+ T cells migrate to the site(s) of infection, where they kill virally infected cells. Early-responding B cells produce and release virus-specific immunoglobulin M (IgM) antibodies; CD4+ T helper cells promote class-switching of germinal center B cells from IgM to IgG or IgA antibodies, and release virus-specific antibody production. After virus clearance, a pool of memory B cells remain and are rapidly reactivated upon reinfection with the same virus. Vaccination aims to generate protective adaptive immune memory without the need for a bona fide primary infection.

There remains uncertainty as to whether some SARS-CoV-2–specific adaptive responses can be detrimental. Although clinical validation is needed, recent TCR and BCR repertoire profiling of active and convalescent COVID-19 patients defined signatures associated with disease severity (7, 13). In actively infected patients, highly mutated BCRs and decreased clonal expansion were associated with more severe clinical outcomes, whereas a larger pool of virus-specific naïve B cells in patients correlated with the development of a more effective antiviral immune response (7, 13). Enhanced T1+1 differentiation, loss of the Treg compartment, and associated lack of germinal center formation were recently observed in postmortem analysis of lymph nodes and spleens from patients who rapidly succumbed (within 10 days of respiratory symptom onset) to COVID-19 (14). Alterated proportions of peripheral blood CD4+ T cell subsets, CD8+ T cell activation status, and B cells have also been observed in patients across a broad spectrum of disease severity. In-depth analysis of ~200 immune parameters revealed that disease severity, including severe inflammation and organ failure, correlated with overall lymphopenia (likely due to multifactorial immune dysregulation), with the remaining lymphocytes reflective of highly activated (and potentially hyperactivated) CD4+ and CD8+ effector T cells, low CD4+ Treg cells, and antibody-producing plasmablasts (short-lived plasma cells) expressing the transcription factor T-bet (15).

The underlying determinants of diverse responses to SARS-CoV-2 remain unclear. One potential avenue for future investigation is to evaluate whether prior infection by other respiratory infections, or preexisting immunemediated conditions such as asthma, may enhance susceptibility to SARS-CoV-2 infection. Most studies evaluating adaptive responses to SARS-CoV-2 infection have analyzed infected adults, whereas such studies in children are more limited. Understanding differences in adaptive immune responses between children and adults is an important concern with respect to SARS-CoV-2 because children appear to be less at risk for severe respiratory complications compared to adults, yet they can develop a life-threatening multisystem inflammatory syndrome. This may reflect altered virus recognition by the immune system in children: A recent study comparing antibody specificity in adults and children with SARS-CoV-2 infection observed reduced antibody diversity in children and a skewed response toward S-protein–specific IgG antibodies (7). Studies evaluating the adaptive immune response, clarifying the interplay between T and B cells as well as innate immune responses, and determining correlates of protection will be key to developing strategies aimed at establishing or boosting T and B cell antiviral immunity.

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