Tab 1

T Cell Immunity to COVID-19 Vaccines

Amy Mbacke

Bachelor of Science in Biology

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The rapid development of COVID-19 vaccines stands as one of the most significant biomedical achievements in recent history. Early evaluations of vaccine effectiveness focused mainly on neutralizing antibody (NAb) responses, while cellular immunity received far less attention. However, accumulating data now demonstrate that T cell responses play a pivotal role in protection from severe COVID-19, especially as SARS-CoV-2 continues to evolve. Understanding cellular immunity has become essential for optimizing current vaccines and informing the design of next-generation vaccines (1).

Protective immunity, whether induced through vaccination or natural infection, relies on both humoral and cellular components. Humoral immunity, mediated by antibodies and memory B cells, primarily prevents infection by blocking the virus from entering host cells. High levels of NAbs in the upper respiratory tract can prevent infection acquisition altogether (1).

A major challenge, however, is that the NAb response is neither long-lasting nor broadly variant-resistant. Although mRNA vaccines initially induce strong neutralizing antibody responses, these levels wane substantially within four to six months. Highly transmissible variants such as Omicron also show substantial escape from NAbs. Antibodies recognize conformational epitopes concentrated in the Spike protein receptor-binding domain (RBD) and N-terminal domain (NTD); therefore, mutations in these regions reduce vaccine-induced antibody effectiveness. The combined effects of waning antibody titers and viral evolution require recalibrating expectations: vaccine-mediated protection against infection itself is limited and temporary (1).

In contrast, T cells offer more durable and variant-resistant protection. Memory T cells do not prevent the initial infection because they recognize viral peptides presented on infected cells

rather than free virus particles. Once activated, cytotoxic CD8+ T cells kill infected cells and release antiviral cytokines, while CD4+ T cells support B cell responses and provide additional antiviral functions. Together, these responses work to limit viral replication and prevent progression to severe disease, particularly in the lower respiratory tract (1).

A key advantage of T cells is their broad recognition of viral epitopes. They target short linear peptides that span multiple regions of the Spike protein, not just the heavily mutated RBD and NTD. As a result, studies show that more than 80% of T cell epitopes remain conserved across major variants, including Omicron (1). Memory T cells are also long-lived, with evidence from other viral infections showing they can persist for years or decades.

Growing evidence supports the central role of T cells in maintaining clinical protection. During the Omicron wave, high infection rates occurred despite reduced neutralizing antibody activity; however, vaccines continued to provide strong protection against hospitalization and death. This disconnect between infection rates and severe disease outcomes suggests that T cell immunity remained effective at the population level. Animal studies further support this idea: macaques depleted of CD8+ T cells showed reduced protection following viral challenge, and vaccine breakthrough cases correlated with weaker variant-specific CD8+ T cell responses (1). Together, these findings strongly indicate that durable, variant-reactive T cell responses are essential for preventing severe COVID-19.

Future research must address how to optimize and monitor T cell immunity. One strategy is incorporating additional conserved viral proteins such as the nucleocapsid (N) or membrane (M) proteins into vaccines to broaden T cell responses. Such approaches may support development of pan-betacoronavirus vaccines, providing protection beyond SARS-CoV-2. In addition, it is

important to understand how different T cell subsets, including mucosal tissue-resident T cells in the respiratory tract, contribute to protection. Establishing standardized methods for measuring T cell responses will be essential for identifying immune correlates of protection and improving vaccine evaluation (1).

In summary, while antibodies play an important role in preventing infection, T cells form a more stable and variant-resistant layer of immunity that protects against severe disease. A deeper understanding of T cell biology will be crucial for enhancing current vaccination strategies and guiding the development of future COVID-19 vaccines.

References

1. Wherry, E. J., & Barouch, D. H. (2022). T cell immunity to COVID-19 vaccines. Science, 377(6608), 821–822. https://doi.org/10.1126/science.add2897