In influenza virus infection, antibodies, memory CD8+ T cells, and CD4+ T cells have all been shown to mediate immune protection, but how they operate and interact with one another to mediate efficient immune responses against virus infection is not well understood. In this issue of the JCI, McKinstry et al. have identified unique functions of memory CD4+ T cells beyond providing “help” for B cell and CD8+ T cell responses during influenza virus infection.

Efficient control and clearance of viral infections requires coordinated interactions of several components of the immune system. Over the past 10 years, Susan Swain and colleagues have elucidated several functions of memory CD4+ T cells during influenza A virus (IAV) infection. They demonstrated the role of memory CD4+ T cells in innate immune responses (1, 2), in the enhancement of B cell responses by follicular helper T (Tfh) cells via Signaling Lymphocyte Activation Molecule (SLAM)-associated protein (SAP) expression (3), and in direct antiviral effects via a perforin–mediated cytotoxic mechanism (4, 5). In this issue of JCI, the Swain group, led by Kai McKinstry, systematically transferred memory CD4+ T cells into mice deficient in specific lymphocyte populations and elegantly dissected the mechanisms by which memory CD4+ T cells protect against IAV infection in mice (6). They report three new findings (Figure 1). First, the innate antiviral functions of memory CD4+ T cells are IFN-γ dependent and independent of the pathogen recognition receptor (PRR) pathway (Figure 1A). Second, memory CD4+ T cells enhance B cell responses independently of Tfh cells and germinal center formation (Figure 1B). Third, in addition to mediating effector functions via a perforin-dependent pathway (Figure 1C), memory CD4+ T cells use the same pathway to drive selection of escape mutants for a process that was known to occur in CD8+ T cells (Figure 1D). These new findings are discussed below.

Conflict of interest: The authors have declared that no conflict of interest exists.

Citation for this article: J Clin Invest. 2012;122(8):2788–2770. doi:10.1172/JCI65208.

Memory CD4+ T cells: beyond “helper” functions
Kobporn Boonnak and Kanta Subbarao
Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, Maryland, USA.

In the current study, McKinstry et al. demonstrate the role of memory CD4+ T cells in immune protection from IAV infection. Memory CD4+ T cells protect mice that lack T or B cells, though CD8+ T cells are needed between days 6 and 10 after infection for viral clearance in B cell–deficient mice (6, 9). McKinstry et al. demonstrated that the protection conferred by memory CD4+ T cells in mice that lack both T and B cells is incomplete; therefore, the authors were interested in examining whether the role of memory CD4+ T cells in mediating immune responses against IAV infection is dependent on the presence of memory CD8+ T cells. They observed that memory CD4+ T cells transferred into IFN-γ receptor–deficient mice protected against IAV infection, indicating that memory CD4+ T cells can mediate immune responses independent of memory CD8+ T cells.

Toward a better understanding of memory CD4+ T cell immunity to influenza virus
During primary influenza infection, CD4+ T cells provide help in promoting antibody production by B cells and are required for the generation of cytotoxic and memory CD8+ T cells (7). After the infection is resolved, the majority of effector CD4+ T cells undergo apoptosis, leaving behind a small population of memory CD4+ T cells, which respond more rapidly and effectively during reinfection. Several studies have suggested additional roles of memory CD4+ T cells during influenza reinfection, including enhancement of innate immune responses (1) as well as non-helper antiviral functions (8).

In the current study, McKinstry et al. demonstrated the role of memory CD4+ T cells in immune protection from IAV infection. Memory CD4+ T cells protect mice that lack T or B cells, though CD8+ T cells are needed between days 6 and 10 after infection for viral clearance in B cell–deficient mice (6, 9). McKinstry et al. demonstrated that the protection conferred by memory CD4+ T cells in mice that lack both T and B cells is incomplete;
mice can be protected against low-dose viral challenge but not against high-dose challenge. Memory CD4+ T cells mediated protection against low-dose influenza infection via IFN-γ production independently of other lymphocytes. The authors also found that to clear infection following a high dose of challenge virus, memory CD4+ T cells interacted with naive B cells and CD8+ T cells. The reduction in morbidity and mortality in the recipient mice was convincing, but the reduction in viral titers (expressed as polymerase [PA] gene copies) was very modest, though statistically significant (6). A relatively small change in pulmonary virus titer can be associated with remarkable differences in mortality in IAV infection in mice (10). In agreement with this study, preexisting memory CD4+ T cells have also been shown to correlate with disease protection against influenza challenge in humans (11–13).

Direct role of memory CD4+ T cells in virus infection
Although the most well-characterized function of memory CD4+ T cells during viral infection is the maintenance of B cell and CD8+ T cell responses, several other roles of memory CD4+ T cells have been elucidated in IAV infection (14). Recent studies have shown that memory CD4+ T cells, but not naive CD4+ T cells, enhance the production of multiple innate inflammatory cytokines and chemokines in the lungs of infected mice and lead to early control of influenza virus infection. Interestingly, McKinstry et al. show, in agreement with previous publications, that innate immune responses mediated by memory CD4+ T cells are PRR independent (1, 6). This is important because influenza viruses can evade immune protection by antagonizing key components of the PRR pathway (15).

Memory CD4+ T cells synergize with other lymphocytes
The CD4+ T cells that enter B cell follicles and provide help to B cells are referred

---

Figure 1
Memory T cell functions demonstrated during IAV infection. (A) Memory CD4+ T cells can clear low-dose influenza virus challenge independently of other lymphocytes by production of IFN-γ via a PRR-independent pathway. (B–D) Memory CD4+ T cells act through multiple pathways to mediate protection against high-dose influenza virus challenge. Memory CD4+ T cells mediate antibody production by B cells independently of Tfh cells and germinal center formation (B), can select for influenza virus escape mutants through perforin-dependent cytotoxicity (C), and enhance CD8+ T cell responses (D).
to as T\textsubscript{FH} cells. Following viral infection, T\textsubscript{FH} cells express SAP to direct the formation of germinal centers (16), where they promote the formation of memory B cells and long-lived antibody-producing plasma cells. Memory CD4\(^+\) T cells are superior to naive T cells in providing help to B cells: they promote earlier B cell proliferation, higher antibody levels, and earlier antibody class switching (17–19). Interestingly, McKinstry et al. show that, unlike naive CD4\(^+\) T cells, enhancement of B cell responses by memory CD4\(^+\) T cells is not dependent on a T\textsubscript{FH}-associated pathway.

Priming of CD8\(^+\) T cells by memory CD4\(^+\) T cells during IAV infection has been studied extensively (20–22), but the role of memory CD4\(^+\) T cells as cytotoxic effectors is less certain. This mechanism is similar to that by which CD8\(^+\) T cells select for influenza escape mutants and that this selection requires perforin. This mechanism is similar to that by which CD8\(^+\) T cells select for escape variants (23).

Questions and future challenges

While the work by McKinstry et al. provides novel insights into cellular mechanisms by which memory CD4\(^+\) T cells contribute to immune protection against influenza, several questions remain. Areas that warrant further study include the help in maintaining effective cytotoxic T lymphocyte responses. J Exp Med. 2003;197(6):803–814.


