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ATTRITION OF MEMORY CD8 T CELLS

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Vezys et al.¹ make the interesting observation that it is possible to repeatedly immunize mice in ways that allow for development of high numbers of memory CD8 T cells without depleting pre-existing memory cells specific for other pathogens. This study, which offers promise in developing potent vaccination schemes, is seemingly at odds with work published by us in the 1990's showing a loss in CD8 memory cells after a series of infections.^{2,3} Vezys et al mention that we may have misinterpreted our data because we reported the putative loss of memory T cells as percent rather than total number, but here we represent the data in those studies as total cell number.^{2–4} Fig 1A portrays limiting dilution assay data, a measure mostly of central memory cells, with 3 to 11 determinations per group, and Fig.1B shows determinations with intracellular cytokine and MHC-dimer assays, with 6 determinations per group. They show that losses in memory CD8 cells became statistically significant after a series of viral infections. Virus-induced losses in total body memory have also been reported by *in vivo* cytotoxicity assays, which monitor the ability of T cells to kill antigen-expressing targets in the host.⁵ Others have reported bacteria-induced losses of T cell-dependent immunity to tumors.⁶ These findings differ with the conclusions of Vezys, et al,¹ who examined loss of memory cells after infections with only a single pathogen or after a series of immunizations with vectors encoding the same antigen in a prime-boost immunization scheme.

The relevance of that point rests on the observations that virus-induced type 1 interferon (IFN) mediates high levels of apoptosis of memory T cells early during infections.^{7–10} We previously addressed the question of whether the long term loss of memory cells was a function of this early apoptosis (active attrition) or due to a competition model for niches in the immune system (passive attrition) and concluded that most of the loss in memory cells could be accounted for by active attrition rather than competition.⁵ We doubt that the prime-boost immunization scheme of Vezys et al.¹ would elicit the apoptosis-inducing levels of type 1 IFN that a series of different viruses would, because the homologous immunity elicited to their immunizing antigen inserts would inhibit replication of the vectors. Further, recombinant vaccinia virus (VV) like that used in this study is a poor IFN inducer. An interesting recent paper by Dudani, et al,¹¹ reports a substantial type 2 IFN (IFN γ)-dependent permanent loss of memory CD8 T cells in mice challenged with intracellular bacteria that were strong IFN γ (but not type 1 IFN) inducers. These authors also concluded that the loss of memory cells was due to an active process and not due to competition. This indicates that more than one class of IFN can cause memory T cell attrition.

Vezys et al.¹ state that an argument for memory CD8 T cell stability is a human study showing a half life of 8–16 years for VV-specific CD8 T cells.¹² However, that same study could not detect VV-specific CD8 T cells in 50% of the subjects vaccinated over 20 years earlier. We contend that those data are more consistent with a loss in human memory T cells than of memory cell stability.

We therefore argue that the study of Vezys et al does not refute earlier work showing that a series of infections depletes splenic memory CD8 cells specific to previously-encountered pathogens. It does, however, nicely show how one can avoid such depletion by using a prime-boost immunization scheme with vectors that are not strong IFN inducers.

Reference List

1. Vezys V, et al. Memory CD8 T-cell compartment grows in size with immunological experience. *Nature*. 2008
2. Selin LK, Vergilis K, Welsh RM, Nahill SR. Reduction of otherwise remarkably stable virus-specific cytotoxic T lymphocyte memory by heterologous viral infections. *J Exp Med*. 1996; 183:2489–2499. [PubMed: 8676069]
3. Selin LK, et al. Attrition of T cell memory:selective loss of lymphocytic choriomeningitis virus (LCMV) epitope-specific memory CD8 T cells following infections with heterologous viruses. *Immunity*. 1999; 11:733–742. [PubMed: 10626895]
4. Varga SM, Selin LK, Welsh RM. Independent regulation of lymphocytic choriomeningitis virus-specific T cell memory pools: relative stability of CD4 memory under conditions of CD8 memory T cell loss. *J Immunol*. 2001; 166:1554–1561. [PubMed: 11160196]
5. Kim SK, Welsh RM. Comprehensive early and lasting loss of memory CD8 T cells and functional memory during acute and persistent viral infections. *J Immunol*. 2004; 172 in press.
6. Smith DK, et al. Cross-reactive antigen is required to prevent erosion of established T cell memory and tumor immunity: a heterologous bacterial model of attrition. *J Immunol*. 2002; 169:1197–1206. [PubMed: 12133940]
7. McNally JM, et al. Attrition of bystander CD8 T cells during virus-induced T cell and interferon responses. *J Virol*. 2001; 75:5965–5976. [PubMed: 11390598]
8. Jiang J, Lau LL, Shen H. Selective depletion of nonspecific T cells during the early stage of immune responses to infection. *J Immunol*. 2003; 171:4352–4358. [PubMed: 14530360]
9. Bahl K, et al. Interferon-induced attrition of CD8 T cells in the presence or absence of cognate antigen during the early stages of viral infections. *J Immunol*. 2005
10. Jiang J, Gross D, Nogusa S, Elbaum P, Murasko DM. Depletion of T cells by type I interferon: differences between young and aged mice. *J Immunol*. 2005; 175:1820–1826. [PubMed: 16034124]
11. Dudani R, Murali-Krishna K, Krishnan L, Sad S. IFN-gamma induces the erosion of preexisting CD8 T cell memory during infection with a heterologous intracellular bacterium. *J Immunol*. 2008; 181:1700–1709. [PubMed: 18641306]
12. Hammarlund E, et al. Duration of antiviral immunity after smallpox vaccination. *Nat Med*. 2003; 9:1131–1137. [PubMed: 12925846]

Figure 1.

Total numbers of lymphocytic choriomeningitis virus (LCMV) epitope-specific CD8 T cells per spleen in mice immune to LCMV and subsequently infected with Pichinde virus (PV), VV, murine cytomegalovirus (MCMV), or vesicular stomatitis virus (VSV). Data are reworked from ref^{3,4}. These are controlled experiments where all measurements were taken at the same time after LCMV infection. **A.** limiting dilution assays (LDA), **B.** MHC-dimer or intracellular interferon γ (ICS) assays. Combined frequencies of T cells specific to LCMV-encoded epitopes NP396, GP33/34, and GP276.