Protective CD8$^+$ T cell memory without help

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CD8 T cells are a key component of the host adaptive immune responses that helps to eradicate invading virus and other cell-associated pathogens. The CD8 T cell responses to an acute infection consist of three well defined phases: naïve pathogen-specific T cells (CD8$\text{N}$) become activated and expand resulting in large numbers of effector cells (CD8$\text{E}$); the contraction of these CD8$\text{E}$ into memory cells (CD8$\text{M}$) once the infection is cleared; and the long-term maintenance of these CD8$\text{M}$. If a secondary infection occurs, the CD8$\text{M}$ mount more vigorous and faster responses than CD8$\text{N}$, which help to rapidly and efficiently control the infection. The prolonged maintenance of this pool of antigen-specific CD8$\text{M}$ can help protect from certain infections. Hence, one of the goals of vaccination is to generate CD8$\text{M}$.

CD4 T cell help (T$\text{H}$) is essential for priming CD8 T cell responses to cell-associated, non-inflammatory antigens while being dispensable for responses generated to a variety of infectious pathogens. In several infectious models, T$\text{H}$ is critical for the conditioning and/or maintenance of the CD8$\text{M}$ pool and/or their secondary expansion and differentiation into secondary effectors.

VACV is an orthopoxvirus (OPV) that was used as the vaccine that eliminated human smallpox, a highly lethal disease caused by the human-specific OPV variola virus (VARV). VACV is regarded as the golden standard of a highly effective vaccine. In addition to preventing smallpox, VACV is also effective as a vaccine against lethal mousepox, a disease caused by the mouse-specific OPV ectromelia virus (ECTV). We previously showed that in addition to antibodies, CD8$\text{M}$ induced by VACV immunization can fully protect susceptible mice from lethal mousepox [1], suggesting that the establishment of a CD8$\text{M}$ pool is one of the mechanisms whereby the smallpox vaccine protects from pathogenic OPVs. However, during the course of VACV infection or immunization, the role of T$\text{H}$ for the generation, maintenance and recall responses of the anti-VACV CD8$\text{M}$ remained controversial [2-6]. A possible explanation for these discrepancies may lie in the replicative capacity of the VACV strain used in different studies. Using a non attenuated VACV strain WR as the vaccine and ECTV as the pathogen, and by measuring polyclonal rather than transgenic CD8 T cells responses, we have recently shown that anti-VACV CD8$\text{M}$ generated in the absence of T$\text{H}$ that expand and differentiate into CD8$\text{E}$ are as effective as helped CD8$\text{M}$ in their ability to protect from lethal ECTV infection [7].

Figure 1: Conditioning and maintenance of anti-VACV CD8$\text{M}$ and their protective capability to ECTV infection can develop without T$\text{H}$. The primary CD8 T cell responses to VACV were similar between wild type B6 mice and MHC-II$^{0/0}$ mice. Functional CD8$\text{M}$ were maintained in MHC-II$^{0/0}$ mice even though at lower frequency. When cell numbers are adjusted, the unhelped CD8$\text{M}$ from MHC-II$^{0/0}$ mice were similarly potent at protecting mice from lethal ECTV infection as the helped CD8$\text{M}$ from wild type mice.
specific for the VACV immunodominant determinant TSYKFESV (also an immunodominant determinant of ECTV) declined faster in MHC-II$^{0/0}$ mice. However, most of the activation and memory markers were similar between the TSYKFESV-specific CD8$_{M}$ from wild type and MHC-II$^{0/0}$ mice. Moreover, the unhelped CD8$_{M}$ expanded and generated secondary CD8$_{M}$ when maintained and boosted in the MHC-II deficient environment, and most of the activation and memory markers between the TSYKFESV-specific secondary CD8$_{M}$ from wild type and MHC-II$^{0/0}$ mice were similar.

The ultimate goal of CD8$_{M}$ is protecting from disease. To test the protective potential of the unhelped CD8$_{M}$, we transferred secondary CD8$_{M}$ from wild type and MHC-II$^{0/0}$ mice into B6.D2-(D6Mit149-D6Mit15) LusJ (B6.D2-D6) mice, a B6 congenic mouse strain that is susceptible to mousepox. Importantly, when adjusted to contain similar numbers of TSYKFESV-specific CD8$_{M}$, the unhelped CD8$_{M}$ protected B6.D2.D6 mice as efficiently as helped CD8$_{M}$. Transferring as few as $4.5 \times 10^4$ helped or unhelped TSYKFESV-specific CD8$_{M}$ significantly reduced the virus loads to similar lower levels and fully protected B6.D2-D6 mice from death. Thus, polyclonal anti-VACV CD8$_{M}$ generated in the absence or in the presence of T$_{H}$ are similarly potent at protecting mice from lethal ECTV infection on a per cell basis.

Our results do not necessarily dispute that T$_{H}$ contribute to optimal maintenance of CD8$_{M}$ as the CD8$_{M}$ declined faster in MHC-II$^{0/0}$ mice than that in WT mice. Yet, it is possible that this faster decline was due to the general poorer health of MHC-II$^{0/0}$ mice, which are immunodeficient. Nevertheless, our work clearly shows that T$_{H}$ is not essential for the establishment of functional CD8$_{M}$ or to confer CD8$_{M}$ the capacity to protect from a lethal infection (Figure 1). Because VACV is used as a vaccine in humans, our results may help us to understand how this vaccine induces protective immunity in people.

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