Editorial

Protective CD8+ T cell memory without help

Min Fang and Luis J. Sigal

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 ($CD8_N$) become activated and expand resulting in large numbers of effector cells ($CD8_E$); the contraction of these $CD8_E$ into memory cells ($CD8_M$) once the infection is cleared; and the long-term maintenance of these $CD8_M$. If a secondary infection occurs, the $CD8_M$ mount more vigorous and faster responses than $CD8_N$, which help to rapidly and efficiently control the infection. The prolonged maintenance of this pool of antigen-specific $CD8_M$ can help protect from certain infections. Hence, one of the goals of vaccination is to generate $CD8_M$.

CD4 T cell help (T_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_H is critical for the conditioning and/or maintenance of the $CD8_M$ 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, $CD8_M$ induced by VACV immunization can fully protect susceptible mice from lethal mousepox [1], suggesting that the establishment of a $CD8_M$ 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_H for the generation, maintenance and recall responses of the anti-VACV $CD8_M$ 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 $CD8_M$ generated in the absence of T_H that expand and differentiate into $CD8_E$ are as effective as helped $CD8_M$ in their ability to protect from lethal ECTV infection [7].

Consistent with some previous research, we found that wild type B6 mice and MHC-II-deficient mice ($MHC\text{-}II^{0/0}$), which lack MHC-II restricted T_H, mounted similar CD8 T cell responses during the acute phase of VACV infection (i.e. 7 days post immunization), indicating that optimal primary CD8 T cell responses to VACV are T_H independent. After virus clearance, the frequency of $CD8_M$

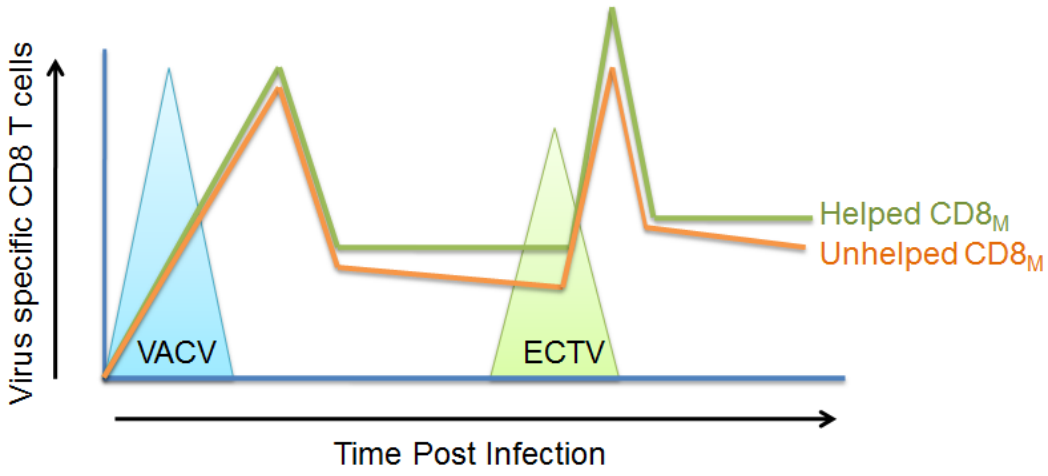

Figure 1: Conditioning and maintenance of anti-VACV $CD8_M$ and their protective capability to ECTV infection can develop without T_H. The primary CD8 T cell responses to VACV were similar between wild type B6 mice and $MHC\text{-}II^{0/0}$ mice. Functional $CD8_M$ were maintained in $MHC\text{-}II^{0/0}$ mice even though at lower frequency. When cell numbers are adjusted, the unhelped $CD8_M$ from $MHC\text{-}II^{0/0}$ mice were similarly potent at protecting mice from lethal ECTV infection as the helped $CD8_M$ 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 4.5×10^4 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 immunodeficent. 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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