## The dangers of coinfection

**The efficacy of vaccination can be impaired considerably by even a mild coinfection; many and often conflicting reasons have been proposed for this phenomenon. Welsh and colleagues, in the *Journal of Virology*, use mice transgenic for a T cell antigen receptor specific for the male HY antigen or for virus peptide to determine how viral coinfection perturbs responses. Simultaneous triggering of HY- and virus-specific T cells results in robust responses by both populations; however, if the stimulation of HY-specific T cells is delayed by a few days, the responses to this antigen are lower. The possibility of activation-induced cell death or active killing by death receptors is ruled out; instead, the impairment coincides with the peak of virus-induced type I interferon (IFN-α or IFN-β). Indeed, interferon stimulators such as poly(I:C) also impair the response of bystander HY-specific T cells much like viral infection, but not if the cells lack the receptor for type I interferon. These findings have important implications for the effective generation of vaccine and memory responses.** ***ZF***

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## Remembering to respond

The adapter molecule MyD88 is critical for signaling through most Toll-like receptors and also has an important T cell–intrinsic role in the response to viral infection. In *Blood*, Turka and colleagues use an inducible-deletion model of MyD88 to determine its role at various stages of the immune response to lymphocytic choriomeningitis virus. Varying the timing of MyD88 deletion in $CD8^+$ T cells shows that its expression is critical for the initial survival and accumulation of cells specific for this virus. However, MyD88 is entirely dispensable for the maintenance of memory cells and it is not required for the population expansion of cells in a secondary response. Therefore, MyD88 has different roles at distinct phases of the immune response, which emphasizes the varying signaling requirements of naive and memory $CD8^+$ T cells. *ZF*

*Blood* **117**, 3123–3130 (2011)

## The quality of memory

**CTLA-4 is an essential negative regulator of T cell activation and has an important role in the suppressive function of naturally occurring regulatory T cells. In the *Journal of Immunology*, Rudolph *et al.* show that CTLA-4 also controls the quality of the memory $CD4^+$ T cell pool without affecting its size. Mice treated with a monoclonal antibody to CTLA-4 have a higher frequency of antigen-specific effector $CD4^+$ T cells that produce IFN-γ during a primary immune response. CTLA-4 blockade does not affect the number of memory $CD4^+$ T cells generated but results in a lower frequency of multifunctional $CD4^+$ T cells that produce multiple cytokines (triple producers of IFN-γ, tumor necrosis factor and interleukin 2) and diminished secondary responses. Depletion of $CD25^+$ T cells has an equivalent effect on memory responses, which suggests that naturally occurring regulatory T cells regulate the CTLA-4-mediated differentiation of multifunctional memory $CD4^+$ T cells.** ***IV***

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## Keeping memory alive

The reactivation and homeostasis of memory $CD4^+$ T cells after antigen recall may depend on different signals than those required during the activation and population expansion of naive T cells. In the *Journal of Experimental Medicine*, Croft and colleagues show that the tumor necrosis factor family members LIGHT and HVEM are required for the persistence of memory cells after stimulation with recall antigen. HVEM-LIGHT interactions are dispensable for the immediate reactivity to recall antigen and have no influence on the effector functions of memory cells, but they are required for T cell survival after the recall response is established. HVEM expression in memory T cells is needed to sustain activation of the kinase Akt and maintain the prosurvival molecule Bcl-2 during the late phase of the recall response. HVEM represents the main signaling element in memory T cells, while LIGHT expression on adjacent effector T cells provides the stimulatory signal. *IV*

*J. Exp. Med.* **208**, 797–809 (2011)

## $CD8\alpha^+$ DCs elicit memory

**Dendritic cells (DCs) are potent inducers of T cell priming, but whether specific subsets induce T cell memory remains controversial. In the *European Journal of Immunology*, Campisi *et al.* use an attenuated *Listeria monocytogenes* infection model to monitor the generation of memory cells. Bacteria that lack the secretion protein SecA2 have less access to host-cell cytoplasm, which results in impaired spreading to other cells. This property allows the discrimination of which infected DC subsets confer memory responses after adoptive transfer to naive hosts. Notably, efficient memory formation requires DCs infected with viable bacteria, as phagocytes that engulf and kill bacteria fail to elicit memory responses. Higher frequencies of $CD8\alpha^+$ DCs than of other DC subsets contain viable bacteria and elicit protective memory responses after subsequent challenge. Protective memory generation correlates with production of inflammatory cytokines, including interleukin 1β and tumor necrosis factor. Whether other DC subsets infected with wild-type bacteria can likewise elicit protective memory responses in an inflammatory environment remains a possibility.** ***LAD***

***Eur. J. Immunol.* (16 Mar 2011) doi:10.1002/eji.201041036**

## CXCR3 alters memory responses

Memory formation is influenced by the strength of antigenic stimulation and inflammatory signals. In the *Proceedings of the National Academy of Sciences*, Matloubian and coworkers show that expression of the inflammatory chemokine receptor CXCR3 also affects the generation of memory T cells. CXCR3 expression is upregulated on $CD8^+$ T cells after infection with lymphocytic choriomeningitis virus, which enhances migration towards the splenic marginal zone where viral antigen is concentrated, and IFN-γ induces expression of the CXCR3 ligand CXCL9. T cells lacking CXCR3 expression proliferate less well than wild-type T cells do at later times after infection (days 5–8) and produce fewer terminally differentiated effector or effector memory cells; instead, more central memory $CCR7^+$ cells are formed in the T cell zones of the spleen. Despite their diminished primary responses, CXCR3-deficient mice nevertheless have robust recall immunity because of the enhanced generation of memory cells. Thus, chemokine-dependent positioning of antigen-specific T cells also influences the generation of memory cells. *LAD*

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