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Tickling Memory T Cells

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Shortly after an organism is infected by viruses, type I interferons (IFN I, which includes IFN-α and IFN-β) are induced (*1*). This rapid, nonspecific immune response is critical in limiting the extent of viral spread before antigen-specific responses can more fully control the infection. Type I interferons also augment proliferation and activation of natural killer cells, further enhancing immune defense (*2*). A report by Tough *et al.* in this issue shows that IFN I has a third function; it can also assist in the generation of T cell responses and immunologic memory (*3*).

Injection of mice with IFN I or poly(I:C), an IFN inducer, results in proliferation of T cells. Only one subset of T cells proliferates—the $CD44^{hi}$ T cells (increased expression of CD44 is a marker for activated and memory T cells)—and this proliferation occurs independently of signaling through the T cell receptor (TCR). In other words, IFN I can tickle memory or activated T cells in an antigen-independent manner.

The massive T cell proliferation (especially of CD8 cells) that characterizes viral infections in vivo (*4*, *5*) could in theory result from a number of mechanisms: antigen-driven expansion of specific T cells, stimulation of cell division by cross-reactive antigens, or cytokine-mediated bystander activation (*4–7*). Although functional assays indicate that the contribution of antigen-specific T cells is relatively low [10% or less of the total activated T cells at the peak of the response (*4*, *5*, *8*)], this value may be an underestimate: Studies with TCR transgenic T cells (in which it is possible to directly visualize the antigen-specific cells) show that the transgenic T cells can expand from less than 1% of the population to more than 50% of CD8 T cells after viral infection (*9*). Thus, much of the expansion during viral infections may represent antigen-driven proliferation of specific T cells.

The results of Tough *et al.* (*3*) implicate a second mechanism for cell proliferation: induction by IFN I cytokines. Indeed, CD8 $CD44^{hi}$ cells are the cell type most responsive to IFN I (*3*), and it is this same T cell subset that shows the most striking expansion during viral infections (*3–5*, *8*, *9*). More than 80% of CD8 $CD44^{hi}$ T cells are dividing after either poly(I:C) injection or viral infection (*3*), although overall CD8 T cell numbers do not change substantially after poly(I:C) injection (*3*). This is because IFN I alone results in only a single round of cell division (only a twofold increase), in striking contrast to the 1000- to 10,000-fold expansion of antigen-specific T cells seen after viral infections (*4*, *5*, *8*, *9*). Thus, after a viral infection, such as infection of mice with lymphocytic choriomeningitis virus, it is likely that IFN I induces many CD8 T cells ($\sim 5 \times 10^6$ per mouse) to undergo a single round of division, whereas, by antigen-driven proliferation, a few cells ($\sim 10^3$ per mouse) undergo multiple cell divisions (10 to 13 divisions over a period of 5 to 7 days) so that the total number increases to between 10^6 and 10^7 (*3–5*, *8*, *9*). Does IFN I also play a role in the antigen-driven proliferation? Possibly. Type I IFN has profound effects on lymphocyte trafficking (*10*) and may contribute to mobilization of the specific immune response.

Perhaps the most interesting implication of the results of Tough *et al.* (*3*) is the possibility that IFN I may be involved in the maintenance of T cell memory [reviewed in (*4*)]. The idea that cytokines produced during responses to unrelated antigens can stimulate preexisting memory T cells is not new (*7*), but Tough *et al.* (*3*) provide the first direct evidence that cytokines cause bystander T cell proliferation in vivo. Thus, periodic stimulation with IFN during intermittent viral infections may help to maintain the pool of memory T cells.

IFN-mediated bystander proliferation may not be obligatory for sustaining long-term T cell memory. Nevertheless, the new results (*3*) suggest a potential mechanism for maintaining memory and underscore the hyperresponsiveness of memory T cells to nonspecific stimuli. Memory cells may also be hyperresponsive to other cytokines and to activation of signaling through adhesion molecules (*4*), as well as to signaling through the TCR by cross-reactive antigens (*6*). Thus, memory T cells can be tickled in many ways that are independent of their specific antigens (*4*). This notion is consistent with data showing that some of the memory CD8 T cells are cycling but that CD8 T cell memory persists in the absence of specific antigen (*4*, *11*).

The finding by Tough *et al.* (*3*) that IFN I selectively stimulates memory T cells raises several interesting questions. Does IFN act directly on T cells or through production of other mediators? Do memory T cells have higher affinity receptors for IFN I? In addition to inducing proliferation, does IFN I also preferentially induce an antiviral state in memory T cells in vivo (a nice protection from viruses)? Why was the proliferative response after poly(I:C) injection seen preferentially in CD8 memory T cells and not in CD4 memory T cells? Does this suggest that the rules for maintaining CD4 and CD8 T cell memory are different (*4*)? Does IFN I stimulate memory T cells and natural killer cells by similar mechanisms? Is maintenance of T cell memory impaired in IFN I–deficient mice? Future studies will provide answers to these questions, but the present report of Tough *et al.* (*3*), in addition to describing an interesting property of IFN I, provides another elegant example of how the nonspecific innate immune system interacts with and shapes the specific immune response (*12*).

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