Correspondence

Naive and Memory CD4+ T Cells in HIV Eradication and Immunization

TO THE EDITOR—The recent article by Lewis and colleagues [1] on age and CD4 count at initiation of antiretroviral therapy (ART) in human immunodeficiency virus (HIV)–infected children is an important contribution. The study shows that memory CD4 T cells (TMC) increase more rapidly than naive CD4 T cells, and that the current guidelines on initiating ART may not optimize long-term immunological health of patients. If the study had included more data on the substudy of TMC, they might have observed the important contribution of memory cells to immune reconstitution. We suggest that a further analysis on the memory subpopulation could provide strong evidence on deciding when to initiate ART and, therefore, might result in long-term immunological health.

It is well known that following the resolution of infection, or after successful vaccination, most virus-specific effector CD4 T cells die. This leaves a small population of memory T cells, which ensures that the frequency of virus-specific T cells is greater than it was before priming. In HIV infection, however, after the first viremia, fewer HIV-specific TMC are left, due to viral direct infection of these cells, in addition to programmed effector cell death. Thus, the population of TMC in the first and second viremia determines the anti-HIV activity in an individual, whether in children or adults or in progressors or non-progressors [2–7]. Studying the activity of TMC during ART, as shown in this study, and coordinating TMC activity with the early viremia will be a key to deciding when to initiate ART to benefit patients by reconstitution of anti-HIV immunity.

TMC orchestrate innate, humoral, and cellular immunity to clear the invading pathogen. Compared to naive CD4 cells, TMC have superior capacity to launch a protective response against the invading pathogen in respect to speed, specificity, and recruiting B and CD8 cells against a specific pathogen. Following the programmed fate of immune cells, after a rapid and effective antiviral response (as in the first viremia of HIV infection), infection is resolved and the majority of effector CD4 T cells die, leaving a much smaller population of memory CD4 TMC that persist [4–7]. This process occurs rapidly, since the immune system is poised to abruptly shift from the effector mode to the more benign memory mode shortly after the resolution of a primary response. This rapid shift can itself be pathogenic, however, depending on the clonal development and the specific repertoire of a TMC pool. A balanced or more benign TMC population may never develop in this short interval, provided that the naive T-cell pool is exhausted or destroyed, as occurs in HIV infection. Determining the status of TMC in an HIV infection, particularly in the first and second period of viremia, allows evaluation of the potential contribution of these cells to anti-HIV immunity.

Upon encountering a previously met pathogen, TMC orchestrate multilevel immune responses to destroy a targeted pathogen. The memory of TMC underpins this multilevel antiviral immunity. The secondary effectors derived from TMC precursors are more capable of mediating direct antiviral activity than primary effectors derived from naive CD4 T cells [8]. Importantly, the two types of effector cells, derived from TMC or naive T cells, are distinguishable functionally and phenotypically. How to utilize the memory of TMC to restore or to reconstitute patient anti-HIV immunity after ART is not only a keystone for efficacy of ART but also for protective vaccination against and eradication of HIV.

Despite its complexity, TMC is probably the best-understood immune cell with stem cell properties [9, 10]. Although the population of TMC diminishes with time and may require boosting, our knowledge and techniques developed from the study of hematopoietic stem cells and humanized mouse models may lead to rapid progress in harnessing the memory of TMC to reconstitute patient anti-HIV immunity, and to develop AIDS vaccines that synergize with ART to eradicate HIV.

Notes

Disclaimer. The opinions expressed in this letter are those of the authors and do not necessarily reflect the opinions or positions of the Department of Medicine, Beth Israel Deaconess Medical Center, or Vaccine and Immunotherapy Center, Mass General Hospital, and Harvard Medical School.

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