Comment on "CD4+CD8+ T Cells Represent a Significant Portion of the Anti-HIV T Cell Response to Acute HIV Infection"

Lena Al-Harthi

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Comment on “CD4⁺CD8⁺ T Cells Represent a Significant Portion of the Anti-HIV T Cell Response to Acute HIV Infection”

Frahm et al. (1) demonstrated that CD4⁺CD8⁺ T cells represent a significant portion of anti-HIV responses among patients who naturally control HIV infection. We also found that CD8⁺ T cells that coexpress CD4 on their surface are polyfunctional and highly enriched in HIV-specific responses (2). Frahm et al. did not distinguish between the four subsets of CD4⁺CD8⁺ T cells (CD4⁺CD8⁺, CD4⁺CD8⁺, CD4⁺CD8⁺, and CD4⁺CD8⁺) (3). It is the CD4⁺CD8⁺ subset that is enriched in anti-HIV responses (2, 4). Additional points by Frahm et al. need clarification. First, the origin of CD4⁺CD8⁺ T cells depends on the subset in question. Activation of CD4⁺ or CD8⁺ T cells induces CD8⁺ or CD8⁺ coexpression, respectively (5). Second, gut and peripheral CD4⁺CD8⁺ T cells are different. Gut CD4⁺CD8⁺ T cells express CD8αα (6), and peripheral CD4⁺CD8⁺ T cells express CD8αβ (5). Third, although still incomplete, there is a significant body of literature about their origin, function, and mechanism of action (2–5, 7–11). Naïve CD8⁺ T cells are more efficient in CD4 upregulation than memory cells (8), suggesting that naïve CD8⁺ T cells respond to cognate Ag by inducing CD4, which tags Ag-specific CD8⁺ T cells. β-catenin, a transcriptional coactivator, mediates the de novo expression of CD4 on CD8⁺ T cells and may contribute to their enhanced survival (11). Finally, blocking CD4 on CD4⁺CD8⁺ T cells or MHC class II on APC abrogates their ability to respond to HIV presentation, indicating that CD4 expression is an important component for CD4⁺CD8⁺ T cell responses to Ags (2).

Lena Al-Harthi

Department of Immunology/Microbiology, Rush University Medical Center, Chicago, IL 60612

Address correspondence and reprint requests to Prof. Lena Al-Harthi, Department of Immunology/Microbiology, Rush University Medical Center, Chicago, IL 60612. E-mail address: Lena_Al-Harthi@rush.edu

References


Response to Comment on “CD4⁺CD8⁺ T Cells Represent a Significant Portion of the Anti-HIV T Cell Response to Acute HIV Infection”

Previous studies reported that the double-positive T cell compartment contains HIV-specific responses (1, 2). In our study, we further investigated the characteristics of the CD4⁺CD8⁺ T cell responses and reported 1) the magnitude of the double-positive T cell contribution to the total proliferative and multifunctional response, 2) the presence of these response modalities during the acute phase of HIV infection, and 3) the Ag specificities recognized by proliferating and/or multifunctional cells. Overall, we demonstrated that CD4⁺CD8⁺ T cells were capable of proliferating in response to HIV Ags and contributed the majority of multifunctional T cells during acute HIV infection. We also provided a comparison of all these acute response findings to a cohort of treatment naive HIV controllers.

The data collected by our group indicated that the whole CD4⁺CD8⁺ T cell compartment contains HIV-specific responses (1, 2). In our study, we further investigated the characteristics of the CD4⁺CD8⁺ T cell responses and reported 1) the magnitude of the double-positive T cell contribution to the total proliferative and multifunctional response, 2) the presence of these response modalities during the acute phase of HIV infection, and 3) the Ag specificities recognized by proliferating and/or multifunctional cells. Overall, we demonstrated that CD4⁺CD8⁺ T cells were capable of proliferating in response to HIV Ags and contributed the majority of multifunctional T cells during acute HIV infection. We also provided a comparison of all these acute response findings to a cohort of treatment naive HIV controllers.

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onstrated that activation-induced coexpression of CD4 in CD8 T cells required >3 d of activation with mitogens. In our study, the intracellular cytokine staining assays were performed within hours of stimulation (6 h) and not days. The proliferative responses described in our study were tested after 6 d of stimulation with HIV-1 peptide, and we did not detect significant differences in the frequency of the double-positive T cell populations. This is consistent with Zloza and colleagues’ (2) report that stimulation with HIV or CMV peptides for 7 d does not result in increased CD4 expression among CD8+ T cells. Finally, as Dr. Al-Harthi details, activation-induced coexpression is most pronounced among naive cells (5). As shown in Supplemental Fig. 1B, we focused our attention on the memory T cell compartment and this could have eliminated a potentially significant source of transient CD4 or CD8 coexpression. Therefore, it is our assumption that the HIV-specific CD4+CD8+ T cells described in our study were predominantly double positive at the time of thawing. We agree with Dr. Al-Harthi that we could not clarify whether these cells were double positive at the time of their clones’ emigration from the thymus or if double positivity was acquired following primary Ag stimulation.

We also agree with Dr. Al-Harthi that gut and peripheral immune cells are often quite different and pointed out that our study was restricted to peripheral blood. Thus, in light of the fact that 1) double-positive T cells are far more common in the gut than in the periphery, 2) double-positive T cells have been shown to be infected by HIV, and 3) the gut is an important site of HIV infection, we hope this study and others cited by us and Dr. Al-Harthi will provide the impetus for significant study of the gut resident double-positive T cell response.

Marc A. Frahm,*† Georgia D. Tomaras,*†,‡,§ and Guido Ferrari*†

*Center for AIDS Research, Duke University Medical Center, Durham, NC 22710; †Department of Molecular Genetics and Microbiology, Duke University Medical Center, Durham, NC. 22710; ‡Department of Immunology, Duke University Medical Center, Durham, NC 22710; and §Department of Surgery, Duke University Medical Center, Durham, NC 22710

Address correspondence and reprint requests to Dr. Guido Ferrari, Department of Surgery, Duke University Medical Center, P.O. Box 2926, Durham, NC 27710. E-mail address: gflmp@duke.edu

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