Antigen Load and Viral Sequence Diversification Determine the Functional Profile of HIV-1–Specific CD8$^+$ T Cells

Hendrik Streeck[1], Zabrina L. Brumme[1], Michael Anastario[2], Kristin W. Cohen[1], Jonathan S. Jolin[1], Angela Meier[1], Chanson J. Brumme[1], Eric S. Rosenberg[1], Galit Alter[1], Todd M. Allen[1], Bruce D. Walker[1,3], Marcus Altfeld[1*]

1 Partners AIDS Research Center, Infectious Disease Unit, Massachusetts General Hospital and Division of AIDS, Harvard Medical School, Boston, Massachusetts, United States of America, **2** Center for Disaster and Humanitarian Assistance Medicine, Department of Military and Emergency Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland, United States of America, **3** Howard Hughes Medical Institute, Chevy Chase, Maryland, United States of America

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Abbreviations: CI, confidence interval; CTL, cytotoxic T lymphocyte; HAART, highly active antiretroviral therapy; IC50, 50% stimulatory concentration; IFN, interferon; IL, interleukin; MFI, median fluorescence intensity; MIP, macrophage inflammatory protein; nt, nucleotide(s); PBMC, peripheral blood mononuclear cell; SD, standard deviation; SFC, spot-forming cell; TNF, tumor necrosis factor; WT, wild type

* To whom correspondence should be addressed. E-mail: maltfeld@partners.org

ABSTRACT

Background

Virus-specific CD8$^+$ T lymphocytes play a key role in the initial reduction of peak viremia during acute viral infections, but display signs of increasing dysfunction and exhaustion under conditions of chronic antigen persistence. It has been suggested that virus-specific CD8$^+$ T cells with a "polyfunctional" profile, defined by the capacity to secrete multiple cytokines or chemokines, are most competent in controlling viral replication in chronic HIV-1 infection. We used HIV-1 infection as a model of chronic persistent viral infection to investigate the process of exhaustion and dysfunction of virus-specific CD8$^+$ T cell responses on the single-epitope level over time, starting in primary HIV-1 infection.

Methods and Findings

We longitudinally analyzed the polyfunctional epitope-specific CD8$^+$ T cell responses of 18 patients during primary HIV-1 infection before and after therapy initiation or sequence variation in the targeted epitope. Epitope-specific CD8$^+$ T cells responded with multiple effector functions to antigenic stimulation during primary HIV-1 infection, but lost their polyfunctional capacity in response to antigen and up-regulated programmed death 1 (PD-1) expression with persistent viremic infection. This exhausted phenotype significantly decreased upon removal of stimulation by antigen, either in response to antiretroviral therapy or by reduction of epitope-specific antigen load in the presence of ongoing viral replication, as a consequence of in vivo selection of cytotoxic T lymphocyte escape mutations in the respective epitopes. Monofunctionality increased in CD8$^+$ T cell responses directed against conserved epitopes from 49% (95% confidence interval 27%–72%) to 76% (56%–95%) (standard deviation [SD] of the effect size 0.71), while monofunctionality remained stable or slightly decreased for responses directed against escaped epitopes from 61% (47%–75%) to 56% (42%–70%) (SD of the effect size 0.18) ($p < 0.05$).

Conclusion

These data suggest that persistence of antigen can be the cause, rather than the consequence, of the functional impairment of virus-specific T cell responses observed during chronic HIV-1 infection, and underscore the importance of evaluating autologous viral sequences in studies aimed at investigating the relationship between virus-specific immunity and associated pathogenesis.

The Editors' Summary of this article follows the references.