HUMAN IMMUNODEFICIENCY VIRUS-DRIVEN EXPANSION OF CD4+CD25+ REGULATORY T CELLS, WHICH SUPPRESS HIV-SPECIFIC CD4+ T-CELL RESPONSES IN HIV-INFECTED PATIENTS


Purpose of the Study. HIV infection is associated with a progressive decline in CD4+ T-cell numbers. However, multiple mechanisms of HIV-associated T-cell dysfunction have been described, including reduced HIV-specific lymphoproliferative and cytotoxic T-cell responses and failure to generate proinflammatory cytokines. A CD4+ T-cell subset with regulatory properties has been characterized. These cells, regulatory T cells (Tregs), express CD25 and inhibit the proliferation of T lymphocytes both in vitro and in vivo. This suppression may be antigen specific and cytokine mediated.

Methods. Peripheral blood T cells were obtained from clinically stable, antiretroviral-treated HIV-infected individuals with CD4+ T cells >500/mm³ and plasma HIV RNA <50 copies per mL. These cells were used for extensive flow-cytometric analysis, proliferation and suppression assays, and expression of FOXP3, a transcription factor in Tregs.

Results. HIV-infected individuals had increased numbers of CD4+CD25+ T cells with the phenotypic, molecular, and functional characteristics of Tregs. This expanded population persisted despite long-term viral control. Patient Tregs suppressed CD4+ T-cell proliferation to recall antigens and specific HIV proteins. The proliferative capacity of T cells to recall and p24 antigens significantly increased after the depletion of Tregs. Additionally, these T cells responded specifically to p24 antigen with expression of transforming growth factor β and interleukin 10. It is interesting to note that the suppressive activity by the cell population did not depend on secretion of transforming growth factor β or interleukin 10.

Conclusions. HIV derives expansion of CD4+CD25 regulatory T cells. This regulatory T-cell subset in turn suppresses HIV-specific CD4+ T-cell responses in HIV-infected patients.

Comment. HIV induces an immunodeficiency by depleting CD4+ T cells. However, demonstrable immunodeficiency occurs before the onset of severe peripheral T-cell depletion. A variety of mechanisms have been invoked to explain this process. The present study demonstrates an additional potential mechanism by which HIV subverts immune responses to both HIV-specific antigens and to those of other infectious agents. The expansion of HIV-induced Tregs suggests a mechanism by which HIV induces partial tolerance to its own antigens. Therapeutic strategies aimed at reducing HIV-specific Tregs might allow more effective control of HIV replication. Alternatively, species-specific simian immunodeficiency viruses seem to induce little disease caused by immune silence. Perhaps enhancement of HIV-specific Tregs rather than suppression of them might result in similar tolerance and lack of disease progression in HIV-infected humans.

Joseph A. Church, MD
Los Angeles, CA

CD4+ T CELL DEPLETION DURING ALL STAGES OF HIV DISEASE OCCURS PREDOMINANTLY IN THE GASTROINTESTINAL TRACT


Purpose of the Study. Mechanisms underlying T-cell depletion in HIV infection are not well understood. This depletion has been studied primarily in the peripheral blood and, to some extent, in peripheral lymphoid tissue. However, a large fraction of CD4+ T cells reside in the gastrointestinal tract. The purpose of this study was to identify the effects of HIV infection on activation and depletion of T cells in the peripheral blood, gastrointestinal tract, and lymph nodes.

Study Population. A total of 14 antiretroviral therapy–naive HIV-infected individuals and 7 HIV-uninfected individuals were recruited.

Methods. Peripheral blood mononuclear cells were obtained from venous blood, ileal Peyer’s patches and lamina propria samples were acquired by endoscopy and biopsy, and inguinal lymph nodes were obtained by percutaneous biopsy. Flow-cytometric analysis was conducted on specimens with standard techniques. HIV-specific T cells were analyzed for phenotypic markers. Additional studies were performed for HIV-specific CD8+ T cells and levels of collagen deposition within lymph nodes.

Results. During primary HIV infection, preferential depletion of mucosal CD4+ T cells occurs compared with peripheral blood and lymph nodes. At all stages of HIV disease, most CD4+ T-cell depletion occurs in the gastrointestinal tract. The primary targets for depletion are activated CD4+CCR5+ T cells. Finally, T-cell activation in lymph nodes is associated with abnormal collagen deposition.

Conclusions. These findings define the nature and extent of CD4+ T-cell depletion in lymphoid tissue, particularly that of the gastrointestinal tract. Most CD4+ T-cells in the effector sites of the gastrointestinal tract are activated and express CCR5. This circumstance creates a particularly attractive medium for HIV infection and replication, which occurs most efficiently in activated CCR5+CD4+ T cells. Additionally, it was shown that therapeutic suppression of HIV permits recovery of circulating CD4+ T cells but did not restore CD4+ T cells in the gastrointestinal tract.

Reviewer’s Comments. Intestinal CD4+ T cells are depleted selectively and rapidly in HIV-infected patients. These findings reflect earlier studies in simian immunodeficiency virus–infected macaque monkeys (Science. 1998;280:142–431). All of these studies together demonstrate that HIV induces severe, organ-specific T-cell depletion in a much briefer time frame than previously identified. Although clinical immunodeficiency may not be apparent for
Human Immunodeficiency Virus-Driven Expansion of CD4+CD25+ Regulatory T Cells, Which Suppress HIV-Specific CD4 T-Cell Responses in HIV-Infected Patients

Joseph A. Church

Pediatrics 2005;116;572
DOI: 10.1542/peds.2005-0698AAAA

Updated Information & Services
including high resolution figures, can be found at:
/content/116/Supplement_2/572.2.full.html

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Gastroenterology
/cgi/collection/gastroenterology_sub
HIV/AIDS
/cgi/collection/hiv:aids_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Human Immunodeficiency Virus-Driven Expansion of CD4+CD25+ Regulatory T Cells, Which Suppress HIV-Specific CD4 T-Cell Responses in HIV-Infected Patients

Joseph A. Church

Pediatrics 2005;116;572
DOI: 10.1542/peds.2005-0698AAAA

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/116/Supplement_2/572.2.full.html