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 CCR5 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 (TGF-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 (TGF-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.

Reviewer’s Comments. 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.

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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;280:412–431). 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
Of great importance is the failure of long-term (≥5 years) highly active retroviral therapy to reverse this site-specific T-cell depletion. Additionally, other studies have demonstrated that HIV is consistently detectable in the intestine of HIV-infected patients, even those with no detectable plasma virus. Current therapies are inadequate for clearing the virus from the intestine, a major reservoir of HIV. New therapies aimed at the mucosal immune system will be required to address this issue. Finally, because the intestine is the earliest target for virus infection and T-cell loss, enhancing mucosal immunity will be critical for any vaccine strategy to be effective.

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PREVENTION OF VAGINAL SHIV TRANSMISSION IN RHESUS MACAQUES THROUGH INHIBITION OF CCR5

Purpose of the Study. Topical agents that prevent transmission of HIV across mucosa during sexual activity are urgently needed, because the vast majority of HIV infections are acquired through transmission across mucosal surfaces. However, the mechanisms of HIV entry at vaginal sites of infection are poorly understood. The chemokine receptor CCR5 serves as an essential co-receptor for HIV entry into target cells. Individuals who lack surface CCR5 expression are highly resistant to acquiring HIV infection through the mucosal route. Because viruses that use CCR5 predominate in the early stages of mucosal transmission, it is likely that such transmission selectively involves CCR5. This suggests a strategy by which vaginal transmission might be prevented.

Methods. The chemokine RANTES is a specific ligand for CCR5. The investigators generated an analog of RANTES, PSC-RANTES, that has an N-terminal modification. In vitro PSC-RANTES inhibited propagation of SHIV, a chimeric simian/human immunodeficiency virus. Thirty adult female rhesus macaques were pretreated with varying concentrations of PSC-RANTES intravaginally. The animals were subsequently challenged with SHIV intravaginally and monitored for up to 24 weeks.

Results. All 5 animals treated with the highest dose of PSC-RANTES were protected from HIV infection. Lower doses also proved protective to a lesser extent. Plasma levels of PSC-RANTES were not detectable, suggesting specific local protection against viral infection.

Conclusions. PSC-RANTES, a selective blocker of CCR5, protected rhesus macaques from intervaginal exposure to a highly infectious dose of SHIV, although the topical concentration of PSC-RANTES that was shown to be protective was many times higher than the concentration required to neutralize the same virus in vitro.

Reviewer’s Comments. A safe, simple, and affordable topical microbicide that would effectively prevent vaginal transmission of HIV is desperately needed, particularly in the developing world. This study provides proof of the concept that targeting the co-receptor for HIV entry into target cells, CCR5, is a viable strategy for the prevention of vaginal transmission of HIV. Cost, however, would be a major obstacle to the implementation of this strategy, but it is now clear that HIV can be stopped before it infects the vaginal mucosa.

Infectious Disease
A SYNTHETIC CONJUGATE POLYSACCHARIDE VACCINE AGAINST HAEMOPHILUS INFLUENZAE TYPE B

Purpose of the Study. To demonstrate the safety and immunogenicity of synthetic glycoconjugate vaccine against Haemophilus influenzae type b (Hib).

Study Population. Adults, children, and infants in Camaguey, Cuba.

Methods. The authors established a large-scale good manufacturing protocol for the production of ~100-g batches of polyribosylribitol phosphate (PRP), the Hib capsular polysaccharide. Synthetic PRP (sPRP) conjugated to protein was shown to be capable of binding antibody from the serum of children immunized with commercial Hib conjugate vaccine. sPRP conjugated to tetanus toxoid (sPRP-TT) from 3 different lots was used for immunization experiments in animals and phase I and II clinical trials in humans. The vaccination dose given was 10 μg of sPRP (sPRP/TT ratio 1:2.6 by weight) via intramuscular injection. All clinical trials were double blind and randomized. Single-dose phase I trials of adults (n = 40) and unimmunized children (4–5 y; n = 133) were followed by single-dose phase II trials of 1041 children. PRP-specific IgG and bactericidal activity were measured from subject sera samples 4 weeks after immunization. A total of 139 infants were then enrolled in a multiple-dose phase I trial and received vaccine at 2, 4, and 6 months. Infants (1141) then were enrolled in a double-blind phase II trial and randomized to receive either sPRP-TT, sPRP-TT with aluminum phosphate, or commercial conjugate vaccine (Vaxem-Hib) at 2, 4, 6, and 18 months. PRP-specific IgG was measured by enzyme-linked immunosorbent assay at 7, 18, and 19 months.

Results. No adverse reactions were reported. From single-dose studies, average PRP-specific IgG levels and percent of patients achieving seroconversion were comparable when sPRP-TT was given with or without aluminum phosphate, and both were comparable to commercial Hib vaccine. Three different lots of sPRP-TT vaccine were tested, with no significant differences between them. In multiple-dose trials of infants, 99.7% reached levels of PRP-specific IgG that are considered to be protective (>1 μg/mL), and geometric mean concentrations of PRP-specific IgG were similar to those in infants immunized with commercial vaccine.

Conclusion. The synthetic vaccine was as safe and immunogenic as licensed commercial vaccines that incorporate native polysaccharide.

Reviewer’s Comments. This is the first report of the large-scale production and clinical testing of a synthetic polysaccharide vaccine. The production of conjugate vaccine from a large-scale culture of microorganisms is expensive, time consuming, and variable. The present work is likely to portend developments in other vaccines that are directed against polysaccharide capsular material (eg, Streptococcus pneumoniae, meningococcal group C). Clinical efficacy remains to be established. Some of the published data suggest lower responses in the youngest infants, which would be of concern.

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CD4⁺ T Cell Depletion During All Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract

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