

The challenge of immune control of immunodeficiency virus

Commentary

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When studies of the dynamics of HIV revealed rapid rates of viral clearance, hopes were raised that potent antiretroviral therapy might lead to cure of infection (1). The documentation of long-lived, latently infected CD4 lymphocytes dashed these hopes (2–4). Potent antiretroviral therapy has dramatically changed the morbidity and mortality of HIV disease in developed countries, but the prospect of the cost, inconvenience, and toxicity of lifelong suppressive chemotherapy is daunting. A second hope – the patient's own immunological defenses – has swept through the community of patients and health care providers. Does this represent a therapeutic opportunity or another mirage, easy to visualize by those with hope and desperation but impossible to grasp?

How can patients with established HIV infection – which infects and destroys CD4 lymphocytes (“the conductors of the immunologic orchestra”), with the usual result of fatal immunodeficiency – hope to be saved by their immune response to HIV? Several lines of evidence can be mustered to justify the pursuit of immunological strategies to contain HIV replication and disease.

Stronger immune responses correlate with less aggressive disease course. CD4 cell proliferative responses to HIV antigen, CD8 cytotoxic T-cell responses, and neutralizing antibody levels are all higher in long-term nonprogressors than in patients with progressive disease (5–10). This raises the chicken and egg question about causal relationships; however, the diminution of virus replication after acute infection is temporarily associated with the appearance of HIV-specific cytotoxic T lymphocyte (CTL) effector responses (11, 12). Perhaps more compelling are recent studies with SHIV- and SIV-infected rhesus

macaques that support the contention that CD8 T cells, by mechanisms not yet elucidated, are required for control of HIV replication. With this model, the *in vivo* depletion of CD8 cells by monoclonal antibodies was temporally associated with significantly higher levels of viral replication (13–15). With the recovery of CD8 cells, the SIV levels diminished (14, 15).

The elicitation and maintenance of HIV-specific immunity, however, is not a trivial matter. CD4 memory cell response to HIV antigen is a suicidal act, converting the cell into a permissive target for the pathogen. Prevention of HIV replication protects CD4 cell depletion, and several groups have documented remarkable restoration of lymphocyte numbers and function with potent antiretroviral therapy. In the first months of treatment, large numbers of CD4/CD45RO (memory phenotype) cells appear in the circulation, largely by redistribution from the solid lymphoid tissue (16–19). Over the next several years, CD4/CD45RA (naive phenotype) cells are gradually regenerated, with peripheral expansion in almost all patients and with significant thymic reconstitution contributing in younger patients (16, 17, 20). Restoration of cell numbers is accompanied by the recovery of detectable, functional immune responses to recall antigens (cytomegalovirus, mycobacteria, and others) that dramatically reduce the risk of opportunistic infection (16).

What is less clear is the degree of restoration of HIV-specific immunity. CD4 cell proliferative responses, which in one report are usually extinguished by ongoing HIV infection, appear to be preserved when potent antiretroviral therapy is administered in the first month or so after infection (7). CTL effector and memory T-cell responses persist with ongoing infection; however, these grad-

ually diminish with progressive disease (8–10). Although recovery of lymphocyte numbers and function results from potent antiretroviral therapy, such therapy (which suppresses significant viral replication and, thus, exposure to large amounts of antigen) results in the rapid disappearance of functional immune CTL responses (21–23).

With the recent development of more sensitive and quantitative assays of T-cell immunity, apparently contradictory data have emerged. Despite the disappearance of functional CTLs from the peripheral circulation with potent antiviral chemotherapy, HIV antigen-specific CD8 cells persist, as measured by MHC class I/peptide epitope/tetramer reagents in FACS[®] analysis (24). These apparently contradictory data do not indicate experimental error. Different assays are more likely measuring different lymphocyte populations with varying functions. If so, 3 fundamental questions arise. One, which T-cell functions are critical for the control of HIV replication? Two, which immunologic assays best measure the T-cell functions of interest? And three, which immunizing strategies elicit these desired functions? Regarding the last question, studies are in progress to examine HIV therapeutic vaccines and to pursue autoimmunization by withdrawal of antiretroviral therapy, as exemplified by the report of Ortiz et al. (25) in this issue of the *JCI*.

Answers to these questions are critical both for therapeutic strategies of immunologic control of HIV replication and for the development of effective HIV prophylactic vaccines. We know, both from extensive clinical experience and from a few, well-monitored clinical studies, that withdrawal of potent antiretroviral therapy routinely results in the rapid resumption of disseminated infection with impressive

dynamics of replication (26–30). Are the anecdotes of delayed resumption and dampened viral dynamics presented by Ortiz et al. (25) and others (31, 32) rare exceptions that prove the rule, or are they the first glimpses of opportunities to elicit and characterize the effective immune responses that will transform the management of HIV infection?

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