IMMUNOPATHOGENESIS AND IMMUNE RECONSTITUTION IN HIV DISEASE

At the New York course, Bruce D. Walker, MD, discussed recent findings on the association of HIV-1-specific T-helper-cell response and cytolytic T-cell response in HIV-infected individuals who exhibit control of viremia in the absence of antiretroviral therapy.

Some patients with HIV-1 infection exhibit no apparent disease progression and plasma viremia below limits of detection of available assays in the absence of antiretroviral therapy. Attenuated viruses and host genetic factors account for only a minority of cases of nonprogressing or slowly progressing disease. In many of the cases of long-term disease-free survival, strong cytolytic T-lymphocyte (CTL) responses to infection are maintained throughout the course of infection, suggesting that host immune response can successfully contain HIV-1 replication. It has recently been found that this response is associated with HIV-specific T-helper-cell activity. Continued elucidation of the mechanisms of successful host response to HIV-1 infection may result in effective immune-based therapies and contribute to the development of anti-HIV vaccine.

CTL Response to Infection

Attenuated HIV-1 and such host genetic factors as chemokine receptor polymorphisms that limit the ability of host cells to become infected appear to account for a minority of cases of nonprogressive HIV-1 infection. Studies of HIV-1-specific immune response have shown that neutralizing antibody may be present in low to undetectable levels in individuals spontaneously controlling HIV-1 infection, indicating that antibody response alone is not sufficient to control viral replication.

There are substantial data in a number of viral systems indicating that CTLs constitute a major component in controlling viral replication. Studies in vitro have shown that addition of single CTL clones specific for a single HIV-1 protein to HIV-1-infected CD4+ cell in culture can produce a 10,000-fold decrease in virion production compared with control culture and that no viral replication is observed with removal of CTLs from culture at 14 days. This antiviral effect is initiated by CTL T-cell-receptor-mediated recognition of processed viral protein presented in the context of an MHC class I molecule on the surface of the infected cell. Direct lysis of the infected cell occurs through CTL production of granzymes and perforin; the activated CTL also bathes the local microenvironment with antiviral factors (beta-chemokines and other soluble factors) that can inhibit virions already produced by the infected cell. Studies of viral dynamics indicate a span of approximately 2.5 days between infection of a cell and budding of progeny virions at the cell surface, during which time viral proteins are being degraded and presented at the cell surface. Recognition of the viral antigen by CTLs during this process may result in cell lysis prior to production of progeny virions and, thus, elimination of virus. The ability of CTLs to control infection depends on cell number and activation state. Attempts to restore the CTL immune response in individuals with chronic infection via infusion of HIV-1-specific CTLs have met with only limited success, probably because the infused cells do not achieve the proper activation state in vivo.

Studies of HIV-1-infected individuals have shown that the CTL response occurs early after the acute infection period. In rapid progressors, this response appears to dissipate rapidly shortly thereafter, whereas nonprogressors appear to maintain a strong response broadly directed against multiple viral proteins even in the absence of antiretroviral therapy (Figure 1). With use of a novel technique for quantitating CTLs in peripheral blood, it has very recently been demonstrated that the number of CTLs is correlated with viral load, providing evidence that this immune response is associated with control of viremia. This technique involves staining of HLA class-I peptide tetramers, consisting of streptavidin bearing four MHC class I molecules and viral peptide, that bind to the CTL surface. The labeled complexes can be directly visualized, with flow cytometry providing a rapid and accurate measure of CTL number.

It has recently been demonstrated that the number of HIV-1-specific CTLs is correlated with plasma viral load in patients not receiving antiretroviral therapy.

Role of T-Helper Cells in CTL Response

The demonstration that increased CTL activity and number are associated with control of HIV-1 viremia has led to attempts to identify the mechanisms controlling the activation state and the magnitude of response of CTLs in vivo. Studies in other viral systems have shown that virus-specific T-helper cells are a critical component in effective control of viral replication. These cells are CD4+ cells that recognize antigen on cell surfaces via the T-cell receptor and interaction with
10- to 100-fold increase in production of antiviral beta chemokines by these cells, compared with low-level production in control experiments, indicating that these helper cells are also directly active in limiting spread of infection.

HIV-1-specific T-helper-cell responses appear to occur early in infection and to be lost shortly thereafter in the majority of infected individuals. This loss occurring early in infection represents a dramatic immune system deficit and occurs in the context of preserved specific T-helper-cell responses to such viruses as cytomegalovirus and Epstein-Barr virus. Recently, Rosenberg and colleagues investigated T-helper-cell response in a unique group of infected persons who were maintaining viral loads below the limits of detection without the need for antiviral therapy. Peripheral blood lymphocytes from such individuals were stimulated with HIV-1 antigens and incubated for 6 days; cell uptake of subsequently added tritiated thymidine was measured as an index of helper cell proliferation, with proliferation serving as an index of cell function. Figure 1 shows the

**Figure 1.** HIV-1-specific CTL and T-helper-cell responses in a patient with rapid disease progression and in a patient with nonprogressing infection. The rapid progressor exhibited a rapid CD4+ cell decline, development of AIDS at 13 months after primary infection, and consistently high plasma viral load (>750,000 RNA copies/mL). The nonprogressor remains well at 19 years, with a CD4+ cell count of 1000/μL and viral load <400 RNA copies/mL. **Top,** percent lysis by CTLs specific for reverse transcriptase (RT), Gag, Env, and Nef proteins of HIV-1 in rapid progressor at 3 and 21 months and in nonprogressor at 17 and 18 years. **Bottom,** stimulation index for specific T-helper-cell responses to HIV-1 gp160 and p24 and tetanus antigen, compared with control condition, in rapid progressor and nonprogressor.

T-helper-cell response in a nonprogressor who is spontaneously controlling viremia, compared with a rapid progressor, as can be seen, the nonprogressor exhibits a strong HIV-1-specific T-helper cell response (as measured by stimulation index) to both viral proteins, whereas the rapid progressor exhibits virtually no response to viral proteins and a reduced response to tetanus antigen. Assessment of relationship between viral load and HIV-1
p24-specific helper cell function in 10 subjects showed a highly significant correlation between the two measures (Figure 2). Subsequent investigation showed that CTL response (to gag protein) was significantly correlated with level of HIV-1-specific T-helper-cell activity.

**Association of Early Treatment and T-Helper-Cell Response**

The association between CTL activity and T-helper-cell activity and the absence of T-helper-cell response in progressive infection suggests that loss of or failure to mount and maintain an effective immune response may be explained by infection and depletion of the activated T-helper cells during acute infection. These cells are primary targets of HIV-1 infection, and their loss may result in insufficient activation of CTLs and failure to maintain function of generated CTLs. In an ongoing study, individuals presenting with acute HIV-1 infection are receiving immediate treatment with potent (triple-drug) antiretroviral therapy and are assessed for T-helper-cell activity with the hypothesis that protection of the T-helper-cell population during acute infection may lead to preserved function after the acute phase. The absence of p24-specific helper cell activity during the acute retroviral syndrome and a robust response was observed at 3 months in one of these patients, along with the correlation of viral burden and specific helper cell activity in this individual (Figure 3). During the acute retroviral syndrome, only 3 of 20 patients showed significant specific T-helper-cell activity with a stimulation index of >10. Responses increased in all individuals followed up for 2 months, with 11 of 15 having a stimulation index of 10 to 100. Responses in this range have been observed in 9 of 10 individuals at 6 months and in each of 4 followed for 1 year (stimulation index range at 1 year, 30 to 167). These findings suggest that early potent antiretroviral therapy may serve to permit an effective immune response that is otherwise observed only in individuals exhibiting spontaneous immune system control of infection.

Whether early effective treatment permits an immune response of sufficient quality or magnitude to result in continued control of infection in the absence of continued treatment is currently being investigated at Dr Walker’s institution. The potential for early therapy to contribute to maintained immune system control of infection is suggested by findings in an acute pathogenic HIV-2 model. In one study, infected control animals were dead at 6 months, whereas five of six animals receiving 16 weeks of stavudine treatment remain alive with control of viremia and normal CD4+ counts at 3 years. In individuals with HIV-1 infection, anecdotal reports suggest that early therapy may influence outcome in at least some persons. Reported studies include those of reboinds of viremia after discontinuation of treatment in patients who started therapy early in infection, including one individual in whom the primary infection syndrome recurred but who had no evidence of specific CTL responses at the time of discontinuation of treatment. However, another individual has exhibited strong T-helper-cell and CTL activity and persistent undetectable viremia, despite the presence of latent reservoirs of infectious virus, for 19 months after cessation of a 6-month course of treatment.

Information from studies of the nature of immune response with early treatment may provide help in determining how immune reconstitution might be best attempted in patients with chronic progressive infection. There is some evidence to suggest that some recovery of T-helper-cell function may be observed over the course of years of treatment in individuals with chronic infection, with some recovery of naïve cells in the periphery and lymph nodes having been observed. It is currently being investigated whether there is recovery of naïve cells during prolonged effective therapy that might permit induction of HIV-1-specific helper cell responses through use of a therapeutic vaccine. Investigations of therapeutic vaccination have typically occurred in individuals with high levels of viremia; it is believed that proliferative response of T-helper cells in such patients would be countered by infection of these target cells in the setting of the high plasma viral load. It is also to be noted that although

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*Figure 2. Correlation of HIV-1 p24-specific T-helper-cell function and plasma viral load in individuals with chronic infection (R = .80; P < .006). Adapted from: Science (Rosenberg et al).*
low-level ongoing viral production in individuals with controlled viremia might be expected to stimulate immune system response to viral antigen, suggesting the potential lack of utility of vaccine stimulation, it may be that the level of stimulation in such individuals is too low for maintenance of a specific immune response. There is some evidence, for example, that antibody response to viral components wanes over time in patients in whom viral replication is suppressed.

Studies of immune response with early treatment may provide help in efforts at immune reconstitution in chronic progressive infection

Summary

Long-term spontaneous control of HIV-1 viremia is associated with maintenance of strong HIV-1-specific T-helper-cell and CTL responses. Individuals with chronic infection lacking a strong CTL response have been found to exhibit low T-helper-cell activity. The initial T-helper-cell response is lost during acute infection of most patients, possibly because of infection and depletion of activated helper cells by HIV. Early potent antiretroviral therapy may produce (or protect,) immune responses similar to those observed in individuals with spontaneous control of viremia by protecting activated helper cells during acute infection. This protective effect may allow maintenance of the population of functional HIV-1-specific helper cells and thus maintenance of the HIV-1-specific CTL activity dependent on helper cell function.

It remains to be determined, however, whether patients treated in the acute stage of infection who develop and maintain strong T-helper-cell responses can control viral replication without antiretroviral therapy. Other important issues to be addressed include whether prolonged treatment with potent antiretroviral therapy permits restoration of T-helper cells in patients with chronic infection and/or whether the immune system in such patients can be appropriately boosted to achieve immunologic control of infection.

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Suggested Readings


