Perspective

Elite Control of HIV Infection: Implications for Vaccines and Treatments

Spontaneous and sustained ("elite," or aviremic) control of HIV infection (ie, maintaining HIV RNA to <50 copies/mL in the absence of therapy) appears to occur in approximately 1 in 300 HIV-infected persons, and represents a distinct phenotype among HIV-infected individuals. Through a recently established international collaboration called the HIV Controller Consortium, over 300 elite controllers have been identified and blood samples collected. These ongoing studies will not only examine the immune responses to HIV that elite controllers generate, but will also make use of a newly available approach to defining the genetic basis of disease. Specifically, the consortium is attempting to determine the genetic basis underlying spontaneous control by performing whole genome analysis scans together with functional immunology studies in a large population of elite controllers. The goal of these studies is to provide insights that will help define the crucial parameters present in persons who are able to control HIV infection, similar to the control most people have with Epstein-Barr virus and varicella, namely by holding the virus in check. These findings could assist in the development of vaccines and new therapies. This article summarizes a presentation on spontaneous control of HIV infection and its implications for vaccine development made by Bruce D. Walker, MD, at an International AIDS Society–USA Continuing Medical Education course in New York in March 2007. The original presentation is available as a Webcast at www.iasusa.org.

Progress toward a preventive HIV vaccine has been slow, and after 20 years of focused vaccine research an effective vaccine remains elusive. The greatest hindrance may be the inability to identify immunogens that can generate broadly cross-neutralizing antibodies capable of recognizing the extremely wide variation in target HIV envelope (Env) proteins; indeed, it is doubtful whether a single vaccine could produce a response that protects against the wide variation in Env proteins among potentially infecting HIV strains present within a single individual, much less within a large population. Given that a preventive vaccine is unlikely, important current goals in vaccine development include an alternate approach: identifying vaccines that do not prevent infection but reduce risk of transmission and prevent disease progression should a vaccinated person become infected.

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A variety of data indicate that risk of transmission of HIV is markedly reduced at plasma HIV RNA levels below 2000 copies/mL, a level of viremia at which progression of disease is also slowed. Such a level of viremia could serve as a target for vaccines to reduce risk of transmission and disease progression. Importantly, spontaneous control of HIV infection has been maintained at or below the relative threshold of an HIV RNA level of 2000 copies/mL in some individuals for up to 28 years or longer. Further understanding of these mechanisms could assist in the development of vaccines that augment control of infection, and may also serve to identify new targets for pharmacologic intervention. To this end, there has been a growing focus on understanding host, viral, and immunologic parameters that are associated with effective containment of HIV infection, and a collaborative effort, the International HIV Controller Consortium, involving patients, health care providers, and scientists has been established to focus an international effort to recruit these patients and uncover the mechanisms that account for control.

Working Definitions of Elite and Viremic Controllers

The HIV Controller Consortium focuses on the tail end of the spectrum of viral load in untreated HIV infection, with a particular emphasis on those with undetectable viral loads, an HIV RNA level of below 50 copies/mL by the currently available assays. Individuals who have maintained HIV RNA levels below 50 copies/mL for at least 1 year in the absence of antiretroviral therapy are identified as elite, or aviremic, controllers, and those maintaining levels of 50 copies/mL to 2000 copies/mL are identified as viremic controllers (see Table 1). Using these criteria, the median duration of infection for persons identified thus far is more than 12 years.

Host and Viral Factors in HIV Controllers

With regard to potential host genetic factors in viral control, the HLA class I allele HLA-B*57 and to a lesser extent the HLA-B*27 allele are over-represented among elite controllers and viremic controllers compared with individuals with progressive infection. Among the first 60 elite controllers recruited in Boston, less than half express HLA-B*57, and this is holding true as the effort is expanded with the HIV Controller Consortium. HLA-B*27 is present in approximately one-fifth of patients. Although these findings clearly suggest a host genetic factor in viral control, the HLA-B*57 allele, for example, is still absent in half or more of individuals with elite control. It is not yet understood how presence of these HLA types is mechanistically related to augmented viral control, but data suggest a link between HLA-B*57 and expression of certain receptors of the innate immune system, suggesting the possibility

Table 1. HIV Controller Consortium Definitions of Elite and Viremic HIV Controllers.

Elite Controllers

- Maintain HIV RNA levels below 50 copies/mL
- No antiretroviral therapy for 1 year or longer
- Episodes of viremia are acceptable as long as there are not consecutive episodes

Viremic Controllers

- Maintain HIV RNA levels below 2000 copies/mL
- No antiretroviral therapy for 1 year or longer
- Episodes of viremia are acceptable as long as they represent the minority of all available determinations

Additional information is available at www.elitecontrollers.org.

that innate immune mechanisms mediated via natural killer cells might contribute to long-term containment.

With regard to potential virus factors, a report several years ago documented slowed progression of disease in association with *nef*-deleted HIV mutants in an Australian cohort infected via transfusion from a single donor. Although earlier studies of *nef* in elite controllers have yielded conflicting results, data thus far using full genome sequencing in elite controllers has not suggested an association of augmented control with attenuated virus due to *nef* deletions or other specific viral polymorphisms. In addition, investigators at the Johns Hopkins University have succeeded in showing that replication-competent HIV can be isolated from aviremic controllers. These are promising findings since they suggest that the state of augmented control is not due merely to "wimpy" virus, but that there should be identifiable and potentially replicable mechanisms in humans that permit spontaneous control of replication-competent HIV.

Host Immune Factors

Cytotoxic CD8 + T lymphocytes (CTLs) act to kill HIV-infected host cells during the period when the virus has become uncoated and its components are in the host cell cytoplasm, with these cells being recognized via presentation of viral antigen in the context of HLA class I molecules. HIV-specific CTLs are effective in eliminating infectious virus in tissue culture. The activity of these T cells and the enrichment for particular HLA class I molecules in elite controllers caused speculation that controllers might exhibit increased magnitude or breadth of CTL response to HIV. However, Dr Walker and colleagues found that magnitude of HIV-specific CTL response (as measured by interferon gamma enzyme-linked immunospot [ELISPOT] assay) was actually lower in elite controllers than in chronically infected progressors, with viremic controllers having an intermediate magnitude of response. Breadth of response (number of peptides to which there was response) was also statistically significantly smaller in elite controllers. Preliminary data suggest preferential targeting of Gag in elite and viremic controllers, consistent with the preferential targeting of Gag recently reported in persons with chronic untreated infection who experience augmented control of virmeia. In this same cohort, preferential targeting of Env by HIV-specific CD8 T cells was associated with higher viral load.

These findings make sense from an immunologic perspective. The viral envelope may function as a decoy to evade immune response, accommodating extensive genetic heterogeneity that does not cause a replicative fitness disadvantage to the virus. Thus, immune responses directed against Env proteins may have relatively lesser effect in reducing viral populations. Gag is less flexible in this regard, since Gag mutations can come at the cost of reduced replicative fitness for the virus. In addition, as noted, CTLs recognize processed viral proteins generated in the target cell cytoplasm. When HIV infects a cell, the Env proteins are left on the cell surface and the preformed core proteins, including Gag, are injected into the cell. These proteins are then processed and sent back to the cell surface where they are presented for immune recognition, likely before production of new virions has occurred within the cell. Studies from Dr David Watkin's lab have shown that infected cells become targets for Gag-specific CTL response within hours of infection. In contrast, Env proteins will be similarly processed and presented only after production of new virions within the cell. Env-specific CTL responses do not occur for 24 hours after infection. Many efforts at developing vaccines intended to protect against disease progression have focused on generating Env-specific responses. However, driving the immune response toward Env-specific responses may turn out to favor the virus; driving the immune response toward Gag-specific responses may be a better strategy in terms of achieving long-term control.

Additional studies are needed to characterize the antiviral effect of Gag-specific CTL response. For the study of neutralizing antibodies, the gold standard is the ability to limit virus replication in vitro. Dr Walker and colleagues compared Gag-specific CTL lines with Env-specific CTL lines from elite controllers on the effects of HIV replication in tissue culture, and found that inhibition is consistently better with Gag-specific responses than inhibition with Env-specific responses. It remains to be determined why some individuals have such effective Gag-specific responses and many do not. One potential factor may involve function of CD4 + T helper cells. Comparison of aviremic controllers, viremic controllers, and progressors has shown that aviremic controllers have statistically significantly higher percentages of CD4 + T helper cells and CTLs that produce both interleukin-2 and interferon gamma (IFN-γ) than do either viremic controllers or progressors.

With regard to humoral immune response, studies of autologous and heterologous neutralization of virus derived from aviremic controllers, viremic controllers, and progressors using plasma from subjects in each group showed that levels of neutralizing antibodies were lowest for aviremic controllers.

Next Steps

Elite controllers of HIV infection appear to be a distinct phenotype, and such control appears to involve the cellular immune response. Dr Walker and colleagues believe that the next key advances for vaccine design will come from dissection of the immune responses that account for spontaneous control of HIV. Lessons and advances from the Human Genome Project can contribute to progress in this regard. Based on techniques of the Human Genome Project, the whole genome analysis scan (WGAS) is a new technique that permits rapid automated analysis for short gene segments using single nucleotide polymorphisms as genetic signatures. This type of analysis has permitted definition of disease-related genes with study of as few as 100 individuals. The HIV Controller Consortium has a goal of performing WGAS on 1000 elite controllers and 1000 viremic controllers, along with 1000 progressor controls, to determine the influence of genetic factors on innate and adaptive immunity and durable suppression of HIV.

The estimated frequency of elite controllers is 1 in 300 infected individuals. On the assumption that approximately 600,000 infected individuals in the United States know their infection status, it is estimated that approximately 2000 infected individuals know of their elite controller status. We hope that practitioners who know of such individuals will contact the consortium or encourage patients to contact the consortium for potential inclusion in this project. Participant blood samples will undergo evaluation by WGAS and functional immunology studies.

Conclusion

In Dr Walker's studies, elite control of HIV infection has been associated with a number of factors—expression of HLA-B*57, dominant CTL targeting of Gag, lower total magnitude and breadth of HIV-specific CTL response, variable inhibition of viral replication by CTL of different specificities, increased functionality of CD4+ and CD8+ T cells, and weak neutralizing antibodies. None of these factors alone predicts elite control. Yet, we know that such a level of spontaneous control of apparently infectious virus does occur, and determining what immunologic factors are sufficient to produce such a state appears to be an achievable task. Identifying these immunologic factors could lead to development of vaccines that could prevent disease progression and control viremia in infected individuals to levels associated with a markedly reduced risk of transmission. Such an effect could have a profound impact in containing and contracting the global HIV epidemic. It is hoped that the HIV Controller Consortium studies will lead to identification of the factors underlying elite control. Readers of this article are encouraged to refer patients for this study, through elitecontrollerstudy@partners.org, or by contacting Dr Florencia Pereyra at fpereyra@partners.org. Additional information on this study is available at www.elitecontrollers.org.

Presented by Bruce D. Walker, MD, in New York in March 2007. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Walker in August 2007.

Dr Walker has served as a consultant to Bristol-Myers Squibb, GlobeImmune, and Merck.

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