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Review

Human Immunodeficiency Virus Controllers: Mechanisms of Durable Virus Control in the Absence of Antiretroviral Therapy

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Chronic viral infections can appear in two very different forms: those that are typically immunologically contained after acute symptomatic infection, such as Epstein-Barr virus (EBV), and those that predictably lead to persistent viremia and progressive clinical disease. Human immunodeficiency virus (HIV) infection is typical of the latter and has resulted in more than 20 million deaths worldwide. Here we review a remarkable subset of persons infected with HIV who are able to achieve long-term control of viremia and avoid immunodeficiency without the need for antiviral therapy. We review the contributing role of host genetic factors, innate and adaptive immune responses, and viral factors that may contribute to this phenotype. These individuals indicate that as with other potentially pathogenic chronic viral infections, the human immune system is able to fully control HIV and prevent HIV-associated disease, at least in some individuals. Further understanding of the mechanisms whereby this occurs should yield critical insights for prophylactic and therapeutic antiviral interventions.

Introduction

More than two decades after the discovery of the etiologic agent of the acquired immune deficiency syndrome (AIDS), the global epidemic continues to expand, and more than 60 million persons have been infected worldwide. Despite marked sequence heterogeneity among human immunodefiency virus (HIV) strains, which can be up to almost 40% within the envelope protein, the clinical course of disease is often quite predictable. An initial symptomatic illness that mimics infectious mononucleosis with fever, pharyngitis, lymphadenopathy, and malaise is followed by an asymptomatic period of approximately 8–10 years in untreated persons, during which time there is ongoing viral replication and progressive HIV-mediated loss of $CD4^+$ T cells. Most antiretroviral-untreated individuals eventually develop profound immunodeficiency and die from AIDS-related complications, with time to death being approximately 10 years after becoming infected.

Ultimate control of the HIV epidemic will require prevention of new infections, and as the global epidemic continues to expand, there has never been a greater need for an effective vaccine. Developing an effective AIDS vaccine that prevents infection may not be feasible (Letvin, 2007, this issue of *Immunity*), so current vaccine strategies are focused on protection from disease progression (Pantaleo and Koup, 2004). This strategy could curtail the global epidemic, even if immunized persons became infected, as long as the viral load in the vaccinated individuals remains low enough to prevent subsequent transmission events (Gray et al., 2001).

Remarkably, a state of apparent durable control of HIV replication does occur in a very small percentage of untreated infected persons. These persons are positive by standard HIV antibody tests yet lack measurable virus in plasma by standard clinical assays (i.e., plasma viral loads are consistently below 50–75 RNA copies/mL). As suggested by their now widely accepted name, these "elite" controllers are exceedingly rare, with most estimates indicating that they make up well less than 1% of the infected population (Hubert et al., 2000). Some have now had documented untreated infection for more than 25 years, providing clear evidence that durable containment of HIV in the absence of therapy is possible. Understanding the mechanisms of HIV control in these individuals is likely to provide critical information for current vaccine strategies. Moreover, given the increasing availability of biologic agents that can modify host responses, defining the mechanisms of successful control of a chronic human viral infection in vivo could lead to the development of novel immune-based therapeutic strategies for those persons with otherwise progressive infections.

Here we review what is known, what is assumed, and what is not known about these potentially highly informative individuals. An additional purpose is to outline an unprecedented international collaborative effort among researchers, health care workers, AIDS service organizations, and HIV-infected persons to recruit large numbers of HIV controllers to define the genetic basis for this remarkable ability to durably contain HIV, which will hopefully guide new therapeutic and vaccine efforts.

Prevalence and Natural History of HIV Controllers

The vast majority of untreated HIV-infected individuals exhibit evidence of ongoing viral replication and progressive

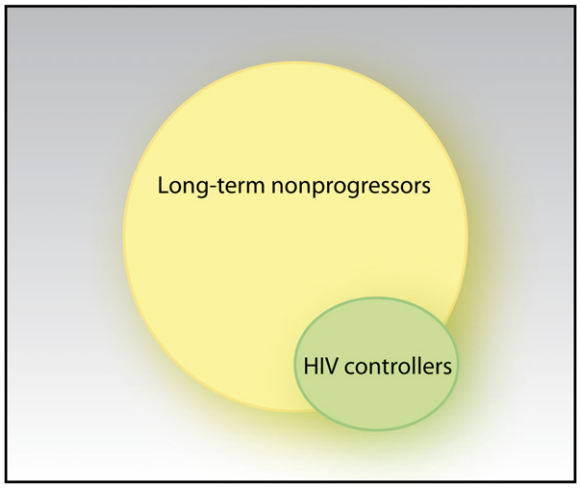

Figure 1. Distinctions between Elite Controllers and HIV Long-Term Nonprogressors

HIV (or "elite") controllers are defined as having undetectable viremia by standard assays (<50 copies RNA/mL) whereas long-term nonprogressors are most often defined by ability to maintain normal $CD4^+$ T cell counts for prolonged periods (>10 years). The prevalence of controllers in most cohorts appears to be much lower than the prevalence of nonprogressors. Although most controllers exhibit minimal rates of $CD4^+$ T cell decline over time, some do progress. Similarly, although some long-term nonprogressors have undetectable viremia, many if not most have viral loads that are low but detectable. Studies aimed at defining mechanisms of virus control should focus on controllers, and studies focused on mechanisms of immunologic progression should also consider $CD4^+$ T cell count outcomes.

$CD4^+$ T cell depletion. However, a small proportion of infected individuals (5%–15%) remain clinically and/or immunologically stable for years (Cao et al., 1995; Munoz et al., 1995; Pantaleo et al., 1995; Sheppard et al., 1993). The term "long-term nonprogressor" was coined for such persons and was generally defined based on duration of infection and $CD4^+$ T cell count, because viral load testing did not become available until the mid-1990s. As viral load testing became available, most long-term nonprogressors were shown to have low to moderate amounts of viremia, and further follow-up revealed that many had progressively increasing viral loads and declining $CD4^+$ T cell counts (Goudsmit et al., 2002; Lefrere et al., 1997; O'Brien et al., 1996; Rodes et al., 2004). At the same time, it became clear that a subset of these individuals was able to maintain viral loads below the limits of detection (<50 copies HIVRNA/mL). These individuals are now often referred to as "elite controllers" or "elite suppressors" and are referred to in this review simply as "HIV controllers" (Figure 1).

Given the importance of understanding the viral-host interaction in these persons, we and others have established the International HIV Controller Consortium and are using the following criteria for enrollment: (1) HIV antibody positive as defined by serologic determinations, (2) no antiretroviral therapy in the preceding 12 month period, and (3) at least three plasma HIV RNA determinations that are taken during this period that span at least 12 months, all of which must be below the limit of detection by currently available clinical assays (50 or 75 RNA copies/mL). Some such individuals have now been infected for more than 25 years, with maintenance of $CD4^+$ T cell counts and persistent viral loads below the limits of detection. Others have subsequently progressed (Hunt et al., 2007), and therefore, close follow-up of large cohorts may allow one to define the parameters associated with control followed by loss of control.

The prevalence of HIV controllers among the HIV-infected population remains poorly defined. In a French cohort of 330 patients with early infection, only 12 subjects (4%) presented with a viral load <200 RNA/mL, but only one (0.3%) had a viral load <20 copies (Hubert et al., 2000). Among more than 2000 individuals identified during early HIV infection in a second cohort, 6.7% had at least two consecutive viral loads below the limit of detection by less sensitive assays (<400 or <500 copies RNA/mL) (Madec et al., 2005a), but the majority of these recently infected individuals eventually exhibited virologic progression (median time to detectable viremia of 3.8 years). In one clinic-based cohort of more than 1300 individuals followed for more than 10 years, only 8 (0.6%) were able to maintain HIV RNA below 400 copies/ml, and in a second related cohort, only 9 of 1551 (0.5%) met this definition (Lambotte et al., 2005). Although none of these studies provide a precise answer, they collectively suggest that durable HIV control occurs in less than 1% of infected individuals.

Epidemiologic factors associated with complete or near complete HIV control in vivo have not been defined. Persons destined to become HIV controllers appear to be less likely to have symptomatic primary infection than those destined to remain viremic (Madec et al., 2005a), suggesting that the complex virus and host interactions that lead to durable control of viral replication are already at play during the earliest phases of HIV disease (Altfeld et al., 2006). The route of HIV acquisition is not associated with the likelihood of achieving an undetectable viral load in the absence of therapy (Madec et al., 2005b) and is likewise not a strong predictor of immunologic nonprogression (Prins and Veugelers, 1997). Gender is also not a limiting factor, with both male and female HIV controllers defined, even though the average plasma HIV RNA "set point" is lower in women than men, independent of all other factors (Sterling et al., 1999). The potential impact of race, geographic location, and/or viral subtype on immunologic and virologic outcomes remains unknown, although controllers have been identified in multiple ethnicities and infected with different virus subtypes.

Potential Antiviral Mechanisms in HIV Controllers

The mechanisms of viral containment in HIV controllers are largely unknown, despite the important implications for current vaccine and therapeutic efforts. Studies thus far have been limited to relatively small numbers of subjects and have variably suggested either virus or host factors as potential explanations, but the precise mechanism or combination of mechanisms accounting for durable virologic control remains elusive.

Attenuated Viruses

There is clear evidence that the pathogenicity of HIV isolates can differ, as shown most conclusively in a group of individuals all infected though blood transfusion from a common donor, all of whom harbored a virus containing a deletion in the *nef* gene and maintained low viremia for years to decades (Deacon et al., 1995). However, many of these persons have since progressed to AIDS (Churchill et al., 2006), arguing that viral attenuation through the *nef* gene does not necessarily lead to life-long control of HIV in vivo. Several small studies and case reports have argued that mutations or deletions within the HIV functional and accessory genes (*rev, tat, vif, vpr,* and *vpu*) can lead to virus control and/or immunologic nonprogression (Alexander et al., 2000; Hassaine et al., 2000; Kirchhoff et al., 1995; Lum et al., 2003; Wang et al., 1996; Yamada and Iwamoto, 2000). Interpretation of most studies of viral attenuation is difficult because they generally include small numbers of patients, involve analysis of viral sequences amplified from peripheral blood mononuclear cells rather than the isolation of replication-competent HIV, often lack a control group of individuals with uncontrolled HIV replication, and almost invariably focused on individuals who had low but detectable plasma HIV RNA.

It has proven difficult to isolate replication-competent virus from HIV controllers. This may be due to exceedingly low amounts of virus in such individuals or the presence of attenuated virus. By using a highly sensitive coculture assay, Blankson and colleagues recently reported successful isolation of replication-competent HIV from 4 of 10 controllers. Virus from these individuals exhibited normal replication kinetics in vitro and lacked any genetic insertions of deletions, suggesting that host rather than virus factors were responsible for durable control (Blankson et al., 2007). The genetic diversity within the *env* gene of plasma virus obtained from individuals in this same cohort was exceedingly low, suggesting limited viral replication and evolution during the entire course of the infection (Bailey et al., 2006a). Collectively, these studies indicate that near-complete host-mediated control of replication-competent virus is possible; whether host or virus factors contribute to control in those without detectable replication-competent virus remains undefined.

Host Genetics

The most consistent host factor associated with virus control is the presence of certain HLA class I alleles, particularly HLA B alleles (Kiepiela et al., 2004). HLA-B5701 and to a lesser extent HLA-B27 are strongly enriched among North American and European cohorts of HIV controllers compared to noncontrollers (Bailey et al., 2006b; Lambotte et al., 2005; Migueles et al., 2000). In addition, the HLA B5703 allele (which is the prevalent B57 subtype in Africans) is similarly highly enriched among African populations who are able to maintain low viral loads (Kiepiela et al., 2007). These observations suggest a causal role for the adaptive immune system because these HLA molecules are involved in immune recognition of virally infected cells. The mechanistic role of HLA-5701 (and presumably other HLA alleles) in the control of HIV remains an open question, however, because (1) HLA-B5701 is in strong linkage disequilibrium with the *HCP5* gene, which may be even more strongly associated with control, although the mechanism for this association is not known (Fellay et al., 2007), (2) HLA-5701-selected escape mutations are not necessarily associated with viral rebound (Bailey et al., 2006b), (3) many HLA-5701-positive individuals with high viral loads lack clear evidence of T cell escape mutations (Migueles et al., 2003), and (4) the HLA-B5701 molecule interacts directly with certain killer immunoglobulin-like receptors, suggesting a genetic component mediated through the innate immune response (Martin et al., 2007), as discussed below.

In addition to genetic factors influencing HIV-specific immune responses, host genetic polymorphisms that affect the ability of HIV to enter cells could have important modulating effects on viral control. Homozygosity for a 32 base pair deletion within the gene encoding CCR5, a coreceptor for HIV entry into CD4-bearing cells, strongly protects against acquisition of HIV, whereas heterozygosity for the *CCR5Δ32* allele is associated with delayed progression to AIDS (Dean et al., 1996). There is also substantial genetic variability within the CCR5 regulator sequences, with some variants being associated with rapid disease progression (Martin et al., 1998).

Although the expression of CCR5 has a clear and central role in HIV pathogenesis, it is only part of a complex story that also involves chemokine receptor ligand expression. *CCL3L1* is a gene that encodes MIP-1α, the most suppressive host ligand for CCR5. The higher the race-adjusted copy number of the *CCL3L1* gene, the lower the steady-state viral load (Gonzalez et al., 2005). When both the *CCR5* haplotype and the *CCL3L1* copy number are combined into genetic risk groups based on risk of developing AIDS or death, the relative absence of a detrimental *CCR5* and *CCL3L1* genotype within HIV controllers becomes striking. Recent data indicate that the mechanism by which these genetic characteristics protect against disease progression is multifactorial and involves restricted viral entry, preserved cell-mediated immunity, and perhaps other mechanisms (Dolan et al., 2007). Other chemokine receptors and/or chemokines receptor ligands (e.g., SDF-1) may also be causally associated with control (Winkler et al., 1998), although this has not been formally tested among HIV controllers.

Innate Immunity

Acute HIV infection is associated with rapid and perhaps irreversible destruction of the extensive $CD4^+$ T cell population that resides in gut-associated lymphoid tissue (Mehandru et al., 2004). In animal models of AIDS virus infection, half or more of the gut-resident $CD4^+$ T cells are lost in the first weeks of infection (Li et al., 2005; Mattapallil et al., 2005). This loss of mucosal integrity results in impaired local cellular immunity (Brenchley et al., 2006) and perhaps chronic translocation of microbial products, which in turn contributes to persistent inflammation (Brenchley et al., 2006). All of these potentially disease-defining events occur before an adaptive T cell response is generated, and therefore the earliest possible influence

of the host immune response is likely mediated by the innate immune response (Pichlmair and Reis e Sousa, 2007, this issue of *Immunity*). Consistent with this hypothesis, a recent series of host genetic studies found that individuals who coexpress KIR3DS1 (a regulatory receptor on the surface of NK cells) and HLA-Bw4-08I (a family of HLA alleles that presumably binds to KIR3DS1 and activates NK cells) have lower viral load set points and reduced risk of progression to AIDS (Martin et al., 2002; Qi et al., 2006). In a recent systematic study of HIV controllers from our cohorts and others, there was a remarkable enrichment of certain natural killer receptors. Strikingly, the effect of HLA B57 on viral load was even greater when expressed in the context of high levels of KIR3DL1, an inhibitory KIR, providing strong evidence that the innate immune response plays a role in disease outcome. This epistatic interaction between HLA B57 and KIR3DL1 may be at least in part explained by the fact that HLA B57 is a Bw4 allele, which is the natural ligand for KIR3DL1. Under normal conditions, the expression of HLA B57 would keep NK cells from lysing these cells during normal immunosurveillance. Were a cell to become infected, this would lead to downregulation of HLA B57 and loss of the NK-inhibitory signal mediated through KIR3DL1. Thus, the break would be released on these NK cells, and lysis of the infected cells could ensue. This mechanism provides a potential explanation as to why persons expressing HLA B57 have less symptomatic acute disease (Altfeld et al., 2003), because NK cells may limit the initial viremia and might also lead to better sparing of tissue-resident $CD4^+$ T cells (Martin et al., 2007). However, functional data on the potential contribution of innate immunity to initial viral control are needed. Polymorphisms in toll-like receptor 9—which mediates innate immune responses against DNA motifs common in viruses and bacteria—have recently been shown to impact the clinical course of disease, further suggesting a link between the innate immune system and disease pathogenesis (Bochud et al., 2007).

Another important component of the innate immune system are the plasmacytoid dendritic cells (PDCs), which produce type-I interferons (e.g., interferon-α), in response to viral infections. HIV, which stimulates these cells via toll-like receptors (Beignon et al., 2005), causes a rapid and sustained decrease in the number of circulating PDCs (Schmidt et al., 2006), presumably because HIV can directly infect these cells (Lore et al., 2005). PDCs are higher in long-term clinical nonprogressors than progressors, suggesting but not proving that these cells can protect against disease progression, although it is possible that their presence may simply be a consequence of low amounts of viral replication (Soumelis et al., 2001).

$CD8^+$ T Cell Immunity

Coincident with the decline in viremia after acute HIV infection, there is an increase in HIV-specific $CD8^+$ T cells that are able to directly kill HIV-infected cells. These observations, plus the consistent association between certain HLA class I molecules and virus control, have contributed to the widely held assumption that effective

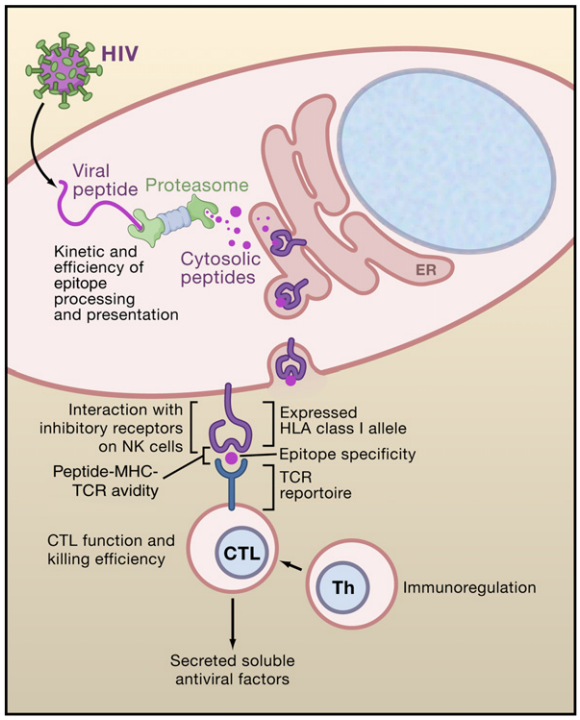

Figure 2. Potential Factors Influencing HIV-Specific CTL and Control of HIV Infection

Specific HLA class I alleles are associated with better disease outcome in HIV infection, suggesting a link to HIV-specific, class I-restricted CTL, but the mechanisms leading to better outcome remain unclear. Possible factors linking class I alleles, CTL, and disease outcome include HLA-associated effects on the efficiency of antigen processing and presentation; Nef-mediated downregulation of HLA alleles, because some expressed class I alleles interact with inhibitory receptors on NK cells and thus would facilitate lysis by the innate arm of the immune response; the avidity of the CTL-infected cell interaction through the peptide-MHC-TCR complex; the TCR repertoire and ability to respond to immune escape variants; the functional ability of cells to kill infected targets; differences in specific soluble antiviral factors released; and the effects of immunoregulatory networks on immune control. Illustration by Andrew Tang.

HIV-specific $CD8^+$ T cell immunity is a dominant factor driving the containment of HIV, but this remains controversial and the mechanism has not been defined (Figure 2). Although there is no clear association between the number of HIV-specific $CD8^+$ T cells (as defined by interferon-gamma production) and virologic control (Addo et al., 2003; Betts et al., 2001), the function of these cells is clearly higher in controllers compared to noncontrollers, including the ability to proliferate upon encounter with HIV antigens (Migueles et al., 2002), the ability to produce the cytolytic protein perforin (Migueles et al., 2002), and the ability to produce multiple cytokines (interferon-γ, MIP-1β, TNF-α, interleukin-2, and/or CD107a) (Betts et al., 2006; Zimmerli et al., 2005). More recent studies show that a virus "neutralization" assay can be used to assess the antiviral potential of $CD8^+$ T cells directly in a manner comparable to that measured with antibody responses. As compared to noncontrollers, freshly isolated $CD8^+$ T cells HIV controllers had higher capacities to inhibit HIV

replication in infected autologous $CD4^+$ T cells (Saez-Cirion et al., 2007). Collectively, these data strongly argue that potent $CD8^+$ T cell responses directed at HIV are causally related to the complete or near complete control of HIV in at least some HIV controllers. Its should be emphasized, however, that many of these studies are by necessity correlative in nature, making it difficult to rule out the possibility that the preservations of potent HIV-specific responses are a consequence rather than a cause of HIV control.

Because of the complexities of studying the immune response in humans, a number of groups have chosen to use the SIV-infected macaque model as a means to more carefully define the immunologic mechanisms for virus control in vivo. As with humans, a small subset of macaques is able to spontaneously control pathogenic SIV infection. These macaques are highly enriched for specific class I alleles (Yant et al., 2006). Antibody depletion of $CD8^+$ T cells in these animals leads to rapid emergence of SIV, arguing that control of the virus is at least partially mediated via $CD8^+$ T cells (and also arguing that these animals were not infected with an attenuated virus) (Friedrich et al., 2007). Of note, the reemergence of effective $CD8^+$ T cells was associated with the re-establishment of virus control, although there was a shift in the immunodominant epitopes.

The enhanced $CD8^+$ T cell antiviral efficacy present in HIV controllers may stem from the ability of certain HLA molecules such as B57 to present a broad number of HIV peptides for T cell recognition, the ability of these molecules to generate high magnitude $CD8^+$ T cell responses (Altfeld et al., 2003; Jansen et al., 2005), and/or the ability of these molecules to preferentially target highly conserved proteins (Altfeld et al., 2003, 2006). With regard to this latter concern, the amount of plasma viremia in chronic infection is inversely associated with the breadth the Gag-specific response and directly associated with the breadth of Env-specific response (Kiepiela et al., 2007). These opposite associations with viral control may be explained by the relative impact of immune-selected mutations on viral fitness. Mutations within Gag may have a higher likelihood of inducing a fitness defect, whereas mutations within the highly variable and pliable Env protein may be less likely to result in substantial growth impairment. This was well illustrated among a cohort of individuals with HLA B*5701, where it was shown that mutations within a highly conserved p24 Gag peptide epitope presented by this allele reduce replicative capacity in vitro (Martinez-Picado et al., 2006) but do not necessarily lead to virologic rebound in vivo (Bailey et al., 2006b). When transmitted to non-HLA B57 individuals, these escape mutations rapidly revert (Leslie et al., 2004), providing strong evidence that these mutations reduce viral fitness in vivo. These observations suggest that HIV is often constrained in its ability to escape selective pressures that target highly conserved and functionally important areas. Vaccine strategies that focus on highly conserved and functionally important regions of the virus could result in either an inability of the virus to escape or the emergence of an escape variant that replicates poorly (Altfeld and Allen, 2006; Goulder and Watkins, 2004).

Alternatively, the enhanced antiviral effect observed for Gag-specific $CD8^+$ T cell responses may have to do with earlier presentation of Gag epitopes on infected cells. Because preformed Gag protein is introduced into the cytoplasm during initial viral entry, it can immediately be processed and presented to CTL. As a result, Gag-specific CTL can recognize infected cells within 4 hr of infection, whereas Env-specific responses are not active until 24 hr, because of the need for de novo protein synthesis for the latter (Sacha et al., 2007).

In summary, these studies provide strong data suggesting that HIV-specific $CD8^+$ T cells may in some patients lead to very efficient inhibition of viral replication. However, it is not clear whether such a response is sufficient or even required. Many HIV controllers lack protective HLA alleles and/or potent HIV-specific T cell responses, while some noncontrollers have these characteristics. Also, durable virus control is often observed even as the virus develops mutations that confer resistance to HIV-specific T cells (Bailey et al., 2006b). Hence, other host and/or virus factors must be involved.

$CD4^+$ T Cell Immunity

An obvious additional host factor modulating control would be $CD4^+$ "helper" T cells, which are required for the long-term maintenance of antigen-specific $CD8^+$ memory T cells (Grakoui et al., 2003; Lichterfeld et al., 2004). HIV is essentially an infection of the immune system, with the major target being $CD4^+$ T cells. In acute AIDS virus infections, there is a massive loss of $CD4^+$ T cells (Guadalupe et al., 2003; Li et al., 2005; Mattapallil et al., 2005), and activated HIV-specific $CD4^+$ T cells are a primary ongoing target for infection (Douek et al., 2002). Early virus-induced loss of those $CD4^+$ T cells that are critical in establishing effective adaptive immune responses is widely believed to be one of the primary reasons humans are not able to successfully control HIV (Douek et al., 2002).

SIV infection of macaques leads to high viremia and rapid disease progression in most but not all animals. As outlined above, experimental depletion of $CD8^+$ T cells in macaques who control SIV replication leads to a rapid rebound in SIV viremia (Friedrich et al., 2007). Interestingly, the subsequent recovery of the immune system was associated with emergence of robust SIV-specific $CD4^+$ and $CD8^+$ T cell responses, which in turn was associated with re-establishment of undetectable or low viral loads (Friedrich et al., 2007), suggesting that both functional antigen-specific $CD4^+$ T cells are indeed required in maintaining the capacity of $CD8^+$ T cells to control viral replication.

Data supporting a role for HIV-specific $CD4^+$ T cells in humans is obviously less direct and based primarily on cross-sectional observations. In a cohort of 30 HIV controllers in San Francisco (CA), the proportion of "polyfunctional" HIV-specific $CD4^+$ that express interferon-gamma (IFN-γ) and interleukin-2 (IL-2) was the single most consistent correlate of control (Emu et al., 2005). Similar trends

toward polyfunctional T cells were observed by others in a group of relative virologic controllers (HIV RNA < 1000 copies/mL) (Harari et al., 2004), in a cohort of nonprogressors (defined based on $CD4^+$ T cell counts) (Boaz et al., 2002), and in elite controllers (Pereyra et al., 2007). Immunoregulatory networks related to $CD4^+$ T cells may play a role in the observed differences. The inhibitory immunoregulatory molecule CTLA-4 is upregulated on HIV-specific $CD4^+$ T cells in all infected subjects except for the HIV controllers, indicating a $CD4^+$ T cell-specific marker associated with viral containment (Kaufmann et al., 2007). Expression of this receptor may diminish the capacity of $CD4^+$ T cells to proliferate in response to HIV peptides or p24 antigen, a function that is maintained in long-term nonprogressors (most of whom had low viral loads) (Martinez et al., 2005; Pontesilli et al., 1999; Rosenberg et al., 1997; Wilson et al., 2000). However, a substantial proportion of HIV controllers—nearly 50%—have no measurable HIV-specific $CD4^+$ T cell activity as determined by cytokine production (Emu et al., 2006; Pitcher et al., 1999). This again indicates that mechanisms other than T cell immunity contribute to durable HIV control.

Humoral Immunity

Another major target for HIV vaccine development is neutralizing antibodies. Most vaccinologists believe that the only way to prevent HIV infection will be to develop a vaccine that can stimulate broadly crossreactive neutralizing antibodies that will recognize circulating strains likely to be encountered. Although older, more labor-intensive, assays suggested that antibodies able to neutralize virus are present in vivo in some long-term nonprogressors (Cao et al., 1995), new high-throughput assays that assess the ability of patient-derived serum to neutralize autologous and heterologous viruses indicate that high-titer neutralizing antibodies are rare in persons who maintain low viral loads in the absence of therapy (Bailey et al., 2006a; Deeks et al., 2006; Pereyra et al., 2007). Moreover, *env* sequences in HIV controllers have small variable loops and few predicted N-linked glycans, both of which suggest limited pressure from neutralizing antibody in vivo (Bailey et al., 2006a). Collectively, these studies strongly argue against humoral immunity as a major mechanism whereby rare individuals are able to achieve durable control of HIV replication in the absence of therapy.

Intracellular Immunity

In recent years, a number of intrinsic intracellular host factors that impair HIV replication have been identified, but whether these play a role in limiting virus replication in HIV controllers remains to be determined. One of these is APOBEC3G, a cellular enzyme that potently restricts HIV replication (Harris and Liddament, 2004). This cytidine deaminase functions primarily by producing massive dG → dA hypermutation of the newly synthesized HIV DNA formed during reverse transcription. HIV circumvents this host defense system via the action of its accessory protein Vif, which targets APOBEC3G for accelerated degradation (Bishop et al., 2004; Sheehy et al., 2002). Another mediator of innate cellular antiviral resistance is Trim 5α, shown to modulate infection in a monkey model of AIDS through a block before the initial step in reverse transcription (Stremlau et al., 2004). Whether genetic variability in these or other yet-to-be-defined host restriction factors may modulate HIV control in humans is unclear.

Immune Activation and Disease Progression

HIV induces a strong and sustained inflammatory response, with as many as 80% of $CD8^+$ T cells in chronic HIV infection expressing cell-surface markers associated with T cell activation. Although the HIV-specific component of this inflammatory response may be beneficial, there is an emerging consensus that much of the inflammatory response is not directed at HIV and that this nonspecific inflammatory response often does more harm than good. Activated $CD4^+$ T cells serve as the primary target of HIV and thus may accelerate HIV disease progression simply by enhancing the ability of the virus to replicate. Perhaps more importantly, chronic nonspecific T cell activation leads to accelerated turnover and death of $CD4^+$ T cells, which in turn may lead to the eventual exhaustion of the immune system's regenerative potential (Grossman et al., 2002; Liu et al., 1998; McCune, 2001). The central independent role of T cell activation in HIV disease pathogenesis is illustrated by the fact that a small percentage (<10%) of HIV controllers exhibit progressive $CD4^+$ T cell loss; this loss occurs despite having no detectable viral replication by standard assays and is associated with markedly elevated $CD8^+$ T cell activation (Hunt et al., 2007).

The degree of T cell activation is lower in controllers than in noncontrollers, but higher than observed in HIV-uninfected individuals and higher than observed in antiretroviral-treated patients (Emu et al., 2005; Hunt et al., 2007). The mechanism for this abnormally elevated T cell activation in HIV controllers is likely multifactorial and includes low amounts of HIV replication, chronic stimulation and expansion of HIV-specific T cell responses, and/or the presence of other coinfections (e.g., CMV). One recent study postulated that HIV-mediated impairment of the gastrointestinal mucosa results in chronic microbial translocation and activation of both the innate and adaptive immune system. Lipopolysaccharide (endotoxin; LPS) amounts—a presumed marker of gastrointestinal bacterial translocation—are also higher in HIV controllers than in HIV-negative individuals and correlate with T cell activation among HIV controllers (Hunt et al., 2007). These observations were surprising because mucosal integrity appears to be relatively intact, at least in the few controllers studied to date (Sankaran et al., 2005).

Compared to noncontrollers, HIV controllers have much lower degrees of T cell activation while at the same time have much higher numbers of HIV-specific T cells (Emu et al., 2005). This balanced response in which the host responds appropriately to a prevalent antigen yet remains relatively quiescent may prove to be the strongest functional correlate of virologic control (Deeks and Walker, 2004). Consistent with this hypothesis, HIV-specific $CD8^+$ T cells from controllers express high amounts of HLA-DR (a presumed activation marker) and are often highly differentiated, even as the general $CD8^+$ T cell

population lack evidence of high-level activation and/or terminal differentiation (Addo et al., 2007; Emu et al., 2005; Saez-Cirion et al., 2007). PD-1, a cell-surface molecule that marks "exhausted" T cells, is generally upregulated in both $CD8^+$ (Day et al., 2006; Petrovas et al., 2006; Trautmann et al., 2006) and $CD4^+$ (Day et al., 2006) T cells in HIV-infected persons but is greatly diminished among HIV controllers (Kaufmann et al., 2007).

Given the deleterious effects of a sustained inflammatory response, the human immune system goes to great lengths to maintain immunologic harmony. Achieving this outcome may be the responsibility of T regulatory cells (Treg cells), a subset of $CD4^+$ T cells that suppress local T cell activation via direct and indirect mechanisms (Thornton and Shevach, 2000). There are conflicting data regarding the role of Treg cells in the immunopathogenesis of HIV disease. Some have argued that these cells prevent or suppress an effective immune response and are therefore harmful whereas others have argued that these cells prevent chronic immune activation and are therefore beneficial. The only published work focusing on the role of Treg cells in nonprogressors found that a relative absence of these cells in the lymphoid tissue was associated with durable virologic control (Nilsson et al., 2006), an effect that was apparently mediated by the preservation of potent HIV-specific T cell responses.

Defining the Genetic Basis for Control of a Chronic Viral Infection: The International HIV Controller Consortium

Although there are multiple factors that may play a role in modulating the degree of HIV viremia, current data indicate that durable in vivo control of HIV cannot be entirely explained by virus or host factors studied to date. Because of the advances of the Human Genome Project, it is now possible to search for novel host genetic factors that influence disease by high-throughput sequencing of single-nucleotide polymorphisms that have been defined within the 3 billion nucleotide human genome (Christensen and Murray, 2007). These types of whole-genome association scans (WGAS) have successfully identified genetic variants that have important roles in common diseases and clinically relevant traits, in some cases with as few as 100 subjects (Plenge and Rioux, 2006). Recently, a whole-genome association scan in persons with different viral load set points after acute HIV infection was reported, revealing two genetic polymorphisms that together account for 15% of the variability in viral load set point (Fellay et al., 2007). Because this type of genetic screen is not biased toward any gene or pathway of known biologic function, this approach has the greatest opportunity to identify factors previously unidentified as important in viral control. To this end, a new international consortium has been established with the plan to recruit 1,000 HIV controllers and perform a WGAS by sequencing 650,000 single-nucleotide polymorphisms within the human genome. The International HIV Controller Consortium consists of scientists, health-care providers, AIDS services organizations, and patients, with the objective of rapidly recruiting persons who fit the HIV-controller definition. To date more than 300 elite controllers have been identified, consent obtained, DNA extracted, and genomic sequencing commenced. These large numbers will allow for haplotypic studies examining the contribution of multiple

Table 1. Potential Mechanisms for Virus Control in HIV "Controllers"

Mechanism	Evidence
Adaptive Immune Response	
HIV-specific $CD8^+$ T cells	Controllers are enriched in certain class I HLA alleles and often have $CD8^+$ T cells that produce multiple cytokines and/or proliferate in response to HIV peptides
HIV-specific $CD4^+$ T cells	Controllers often have $CD4^+$ T cells that express high amounts of HIV-specific IL-2 and interferon-γ in response to HIV peptides
Innate Immune Responses	
Natural killer cells	Controllers are strongly enriched for certain NK cell receptors that are involved in regulating the function of these cells
Plasmacytoid dendritic cells (PDCs)	The number and/or function of PDCs are high in some controllers
Reduced cellular entry	Controllers are enriched for genetic polymorphisms in the CCR5 pathway associated with reduced amounts of this viral coreceptor and/or have high amounts of CCR5 ligands that may compete with HIV for cell entry
Immunoregulation	
T regulatory cells	T regulatory cells—which blunt antigen-specific T cell responses—are low in some HIV controllers, particularly in lymphoid tissues
Attenuated viruses	Some controllers harbor viruses containing mutations and/or deletions in key regulatory or accessory genes, particularly *nef*
	Mutations induced by $CD8^+$ T cell pressure leading to reduced viral fitness

factors mentioned above that appear to contribute to durable and perhaps indefinite control of HIV replication.

Conclusions

Long-term containment of an otherwise chronic progressive infection provides hope for successful control of HIV and other chronic viral infections such as HCV. Because most vaccines protect against disease rather than against infection, it is critical to understand the mechanisms of natural viral control in those rare cases in which this occurs. Indeed, HIV controllers who maintain viral loads below the limits of detection exhibit a degree of control that would lead to contraction of the global epidemic, because of both decreased progression and decreased risk of transmission. Data thus far generated from small studies indicate a high association between virus control and the presence of certain host HLA class I alleles and $CD8^+$ T cell responses generated through these alleles, as well as strong virus-specific $CD4^+$ T cell responses. The collective data outlined here, however, illustrate that no single factor thus far defined is completely protective; nor, for that matter, is any one factor strictly required (Table 1). Just as large, well-designed studies have been needed to carefully define which combinations of drugs work best for the therapeutic management of HIV infection (Hammer et al., 2006), we believe that large, well-designed studies are needed to define which combinations of host factors are most likely to result in such remarkable virus control. Efforts are now underway to develop the large cohorts necessary to initiate such work.

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