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Elite control of HIV: is this the right model for a functional cure?

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A cure for HIV is still greatly needed and has become a global research priority. A unique subset of HIV-infected individuals who spontaneously control HIV exists, and these are known as 'elite controllers'. They may represent a natural model for a 'functional cure' in which there is long term control of viral replication and remission from symptoms of HIV infection in the absence of antiretroviral therapy. However, controllers have evidence of ongoing inflammation, $CD4^+$ T cell depletion, and perhaps even inflammation-associated cardiovascular disease, suggesting that this natural long term virologic control may be coming at an immunologic and clinical cost. These individuals may continue to provide continued insights into mechanisms of host control; however, they may not represent the best model of a functional cure, if we believe that a cure should require a disease-free (and not just a treatment-free) state.

HIV cure is a research priority

The use of antiretroviral therapy (ART) has resulted in the marked decline in the morbidity and mortality associated with HIV infection for individuals with access to therapy [1,2]. Many antiretroviral-treated individuals achieve substantial reconstitution of $CD4^+$ T cell counts and near-complete suppression of viral replication. However, despite this achievement, ART is not curative. Interruption of therapy results in the rapid rebound of viral replication in most HIV-infected individuals due to the presence of a long-lived infected cell population that harbors replication-competent virus known as the latent viral reservoir (see Glossary) [3]. Furthermore, even in those individuals who are successfully treated, ART does not fully restore health or normal immune function as HIV-infected individuals still experience increased non-AIDS-related morbidity and mortality compared to HIV-uninfected individuals [4–7]. Lastly, there are still a large number of individuals who do not have access to ART, which contributes to morbidity and subsequent transmission events [8,9]. Therefore, there is a great need for a cure for HIV infection and this has become a global research priority [10].

A cure may be feasible and elite controllers may be a potential model for functional cure

The case of the 'Berlin patient' has provided evidence to suggest that a cure for HIV infection may be possible in some individuals [11]. The Berlin patient is thought to have achieved a 'sterilizing cure' given that no replication-competent virus has been found, despite vigorous study several years after the discontinuation of ART [12,13]. The circumstances which led to this apparent cure were incredibly unique, however, because this patient: (i) was heterozygous for the CCR5 delta-32 (Δ32) deletion at baseline (a genetic factor known to confer a favorable HIV disease course); (ii) received an extensive conditioning regimen that included whole body irradiation to deplete the hematopoietic system; (iii) received two allogeneic bone marrow transplants from a donor who was homozygous for the CCR5 Δ32 deletion; (iv) exhibited graft-versus-host disease (and perhaps as a consequence 'graft-versus-HIV-reservoir responses'); and (v) received immune-modulating therapies after transplant. It is unclear whether one, or all, of these factors was necessary to achieve a sterilizing cure. Furthermore, many of the interventions in this unique case have substantial risks associated with them, making this scenario difficult to replicate in a wider population. A sterilizing cure, therefore, is likely to be more difficult to achieve and may not be possible for most HIV-infected individuals.

There exists a population of HIV-infected individuals who spontaneously control their virus, termed 'HIV controllers'. This group may represent a natural model for a 'functional cure' in which there is long term control of viral replication and remission from symptoms of HIV infection in the absence of ART. It is likely that a functional cure will be more feasible than a sterilizing cure. Understanding the

Glossary

Elite controller: a subset of HIV-infected individuals who maintain plasma viral loads to levels below the limits of clinical detection (<50–75 copies/ml) in the absence of anti-retroviral therapy.
Functional cure: long term host control of viral replication and remission from symptoms of HIV-infection in the absence of ART, but replication-competent HIV remains detectable.
Latent viral reservoir: an HIV-infected cell population that harbors integrated, replication-competent HIV virus.
Long term nonprogressors (LTNPs): individuals with long term clinical and immunologic stability, usually over a period of several years, in the absence of ART. These individuals may or may not have a low HIV plasma viral load as there is usually no viral load requirement in this definition.
Sterilizing cure: complete eradication of replication-competent HIV from the body.

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biologic mechanisms of HIV control is an area of intense research focus as it may inform future therapeutic strategies.

Defining elite control

HIV controllers are HIV-infected individuals who, in the absence of therapy, are able to maintain low levels of plasma HIV RNA. They are often distinct from 'long term nonprogressors' (LTNPs) who are generally defined as untreated individuals who have long term clinical and immunologic stability over a period of several years, without a viral load requirement. The term 'elite controllers' usually refers to the subset of controllers who maintain plasma viremia to levels below the limits of clinical detection (<50–75 copies/ml). This a rare group, comprising <1% of the HIV-infected population [14]. There is an over-representation of certain MHC class 1 alleles in elite controllers, including class I HLA-B*57 and HLA-B*27 alleles [15–17]. Enrichment of specific natural killer (NK) cell immunoglobulin-like receptors (KIR) has also been seen in one study of LTNPs [18], although this finding was not seen in a small cohort of elite controllers [19]. These data argue that sustained host immune responses are a mechanism by which virus is controlled in these individuals. However, not all HIV controllers possess these protective alleles, and some individuals with favorable genetics have normal progression of disease, suggesting that these genetic factors are neither necessary nor sufficient for immune control [20]. Thus, elite controllers are likely a heterogeneous group with multiple potential mechanisms of control and this group of individuals provides a unique opportunity to better understand viral persistence and host control.

Potential mechanisms of viral control

The precise mechanism of viral control in elite controllers is unknown and may be multifactorial with different factors playing a role in different individuals [21]. Host genetics and how they shape the response of the different arms of the immune system: adaptive, innate, and intrinsic, are all possible areas in which elite controllers may have unique ways to maintain control of viral replication (Figure 1).

One potential mechanism of control is the $CD8^+$ T cell response. The presence of specific MHC class 1 alleles has been one of the most consistent factors associated with host control. It may be that $CD8^+$ cytotoxic T lymphocytes (CTLs) restricted by the class I molecules such as HLA-B*57 and HLA-B*27 are more potent and polyfunctional [22–24]. Previous studies have found that although the frequency of HIV specific $CD8^+$ CTLs is not elevated in elite controllers [25], their CTLs seem to produce more cytolytic proteins, such as perforin and granzyme B, [23,26] and more pro-inflammatory cytokines, including interleukin (IL-2) and interferon-gamma (IFN-γ) [24]. However, a strong CTL response is unlikely to be the only factor leading to viral control, as elite controllers have been shown to maintain viral suppression even in the setting of viral escape mutations [27].

The role of antibodies in achieving viral suppression in elite controllers is unclear. Several studies have shown that the levels of neutralizing antibodies (antibodies that bind to the HIV envelope and block viral entry into target cells) are either similar or lower in elite controllers compared to viremic individuals [28,29]. However, antibodies could also contribute to viral control via antibody-dependent cell-mediated cytotoxicity (ADCC). In ADCC, cells coated with antibodies are destroyed by NK cells. It is unclear, however, whether elite controllers have increased ADCC activity, as studies have had conflicting results [28,30].

Another mechanism by which elite controllers may achieve viral suppression is via the innate immune system. HLA class 1 molecules can also bind to KIRs that are expressed by NK cells. HLA-B*57 is a Bw4 allele, which is a natural ligand for several KIRs including KIR3DS1 and KIR3DL1, and this combination has been associated with delayed progression to AIDS in noncontrollers [31,32]. It is possible that this relationship is explained by linkage disequilibrium with HLA-B alleles, but a previous study found that these KIRs were enriched in a population of LTNPs who did not possess the HLA-B*57 allele [18]. NK cells expressing the KIR3DS1 allele strongly inhibit HIV replication in target cells *in vitro* and may be a mechanism of elite control apart from its association with HLA-B alleles [33]. Further studies are needed to better understand the contribution of KIRs to viral control in elite controllers.

The intrinsic immune system may also play a role in the control of HIV in elite controllers. Cell-intrinsic mechanisms, such as restriction factors, can limit HIV's ability to replicate in target cells and could theoretically lead to control of plasma viremia. However, one study which looked at one of the most well-characterized restriction factors, APOBEC3G, did not find a higher frequency of hypermutated proviral genomes in elite controllers compared to ART-treated individuals, suggesting that enhanced APOBEC activity alone could not account for the control of viral replication in elite controllers [34]. Another recent study examined 34 anti-HIV host restriction factors and did not find an increase in the overall expression of restriction factors in elite controllers [35]. However, a single factor, schlafen 11, was expressed at a significantly higher level in $CD4^+$ T cells from elite controllers compared to both untreated and ART suppressed subjects. It may be that the expression of specific host restriction factors, rather than the overall frequency of expression, is important for viral control. Additional examination of restriction factors could lead to the development of curative strategies.

Translating mechanisms of viral control to cure research

There are potentially several factors that allow elite controllers to maintain undetectable viral loads and that may be relevant for cure research. These factors include $CD8^+$ CTL responses, KIRs, and intrinsic restriction factors. Eliciting strong CTL responses will likely be a part of future cure strategies. Recent cure efforts have focused on reactivation strategies; however, a recent study found that reactivation alone in the presence of autologous $CD8^+$ T cells did not result in effective killing [36]. Prestimulation of $CD8^+$ T cells or using CTLs from elite controllers