Elite controllers as a model of functional cure

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Purpose of review

The limitations of life-long antiretroviral therapies for the HIV infection lead to a novel concept of a functional cure developing innovative therapeutic strategies to generate a long-term remission of HIV replication without treatment. This concept requires an understanding of the mechanisms by which HIV is controlled in conditions of undetectable virus replication, before developing ambitious therapies blocking durably viral replication – and ultimately eradicating HIV.

Recent findings

Recent literature shows that the exceptional elite controller status is usually not driven by virus gross genetic defects, despite some virus attenuation resulting from immune selective pressure, but is frequently determined by host's genetic factors permitting robust cell-mediated immunity to control the virus replication and reservoirs. Lack of immunity and immune deficiency can however limit this model in some cases and only a subgroup in whom both the virus and the immune deficiency are controlled, that is the elite long-term controllers, might represent the best current model for a functional cure.

Summary

This review examines whether the exceptional HIV-infected elite controllers, who spontaneously and durably maintain extremely low virus replication, might be considered as a model for a functional cure and whether the mechanisms identified in these exceptional individuals might serve to identify therapeutic or vaccine strategies.

Keywords

elite controllers, genetic markers, HIV cure, HIV reservoirs

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Introduction

The concept of a functional cure has emerged in the last 2 years as the long-term sustainability of long-life antiretroviral therapies became an essential, but obviously, problematic issue. This limitation requires that development of more ambitious treatment options. Functional cure is usually understood to be achieving, with an appropriate therapeutic strategy, a long-term remission – that is a persistent control of HIV infection – without the need for sustained treatment in patients who do not spontaneously control the virus. Functional cure could also be merged with the concept of a sterilizing cure of eradication of HIV from an infected person. This ultimate goal appears to be legitimised by the unique case of the 'Berlin' patient who achieved stable virus undetectability after haematopoietic stem cells (HSCs) grafts from a CCR5-deficient donor [1••]. The HIV cure concept also became more attainable with the ability of the most modern drug combinations to achieve sustainable virus undetectability in most patients, though without completely eliminating the virus nor preventing replication relapses if therapy is interrupted. On the other hand, as hope for an HIV vaccine was partially restored by the modest success of the Thai vaccine trial [2], a reasonable objective for vaccines remains to allow long-term virus control, i.e. a functional cure. Long-term treated patients or HIV-infected vaccinees would therefore resemble those extraordinary patients, usually referred as natural suppressors [3,4], HIV controllers [5,6], or elite controllers who [7] maintain a full control of the virus by means of their own defenses. Understanding the mechanisms by which the virus is controlled in these exceptional individuals thus becomes an even more demanding objective in order to identify therapeutic or vaccine strategies that may ensure lack of viral replication, despite viral persistence, and ultimately viral eradication.

The purpose of this review is to analyze to what extent elite controllers represent a model of a spontaneous functional cure of the HIV infection and open avenues for

developing therapeutic strategies to achieve a functional cure. What can be learned from these specific populations of elite controllers? To what extent this exceptional status is genetically driven? What are the immune mechanisms of persistent control of the infection and/or disease? How are characterized viral reservoirs in those populations: Which cells under which conditions contribute which roles to the reservoirs? What are the mechanisms for reservoir maintenance or HIV latency in different cell types? How can these informations be used to designing therapeutic strategies for a functional cure?

What is a functional cure?

The only evidence so far that a cure from HIV is plausible comes from the unique case of an HIV-infected patient in whom viral replication remained undetectable despite discontinuation of antiretroviral therapy after transplantation with CCR5Δ32/Δ32 HSCs that had ensured successful reconstitution of long-lived $CD4^+$ T cells of donor origin. Although proving full eradication of the virus remains elusive, the lack of detectable HIV-RNA or HIV-DNA copy in any compartment 45 months after treatment arrest, despite CD4 T cells are fully susceptible to X4 viruses, defines at the minimum 'a functional cure' and at the best 'a sterilizing cure' [1••,8••]. In addition, although HIV-specific T cells are not reported, the decrease to low levels of HIV-envelope-specific antibodies defines for the first time the immune stigmatas of a recovery.

Such an extreme concept of a cure might be unrealistic and one should understand 'Functional Cure' as a long-term remission of virus replication and HIV-related symptoms in the absence of antiretroviral therapies, even when HIV provirus remains detectable.

This definition remains extremely vague yet and bypasses the recent drawbacks observed when interrupting therapy. Indeed the SMART study reports that HIV replication, even minimal, can cause severe tissue damages reflecting HIV-related immune activation [9], while the failures of 'Structured Treatment Interruptions' at inducing long-term remissions during the early 2000s [10] illustrate the need for more stringent strategies. Nevertheless, several programs have been set up to reach a functional cure by developing a wide array of therapeutic strategies and have popularized the concept of a functional cure [11,12•,13•]. We recently reported cases of long-term viral control after interruption of a treatment initiated at the time of acute infection [14]. Those patients are characterized by sustained normal $CD4^+$ T-cell counts, low HIV reservoir levels and lack of protective HLA alleles, although the mechanism of such control still remains unknown.

Key points

- Low-level virus replication is evidenced in some elite controllers; nevertheless, there is no evidence of high level of defective virus.
- In elite controllers, over-represented heterozygous CCR5 gene Δ32 deletion might limit but does not inhibit virus entry, while peculiar MHC class I alleles, particularly HLA-B∗57, promotes robust antiviral CD8 T-cell-mediated immunity, but does not result in a sterilizing cure.
- CD8 T-cell responses to HIV are generally strong and mediate potent antiviral cytolytic activity, but their absence in some elite controllers does not appear to affect virus replication.
- The stable elite controllers' HIV reservoir is extremely low, strongly linked to the host's MHC alleles and CD8-specific T cells but does not differ from those of long-term suppressed patients under antiretroviral therapy initiated at the time of the primary infection.
- Few elite controllers do show progressive immune deficiency or tissue alterations resulting from immune activation and finally only a small proportion (elite long-term nonprogressors) might represent models of functional cure with long-term virus undetectability and stable immune competence.

Are elite controllers a model for a functional cure?

Rare HIV-infected individuals controlling viremia below the limit of detection without antiviral therapy were described using various cutoffs (<500 or 50 copies of HIV-RNA/ml) and different lengths of follow-up, usually at least 10 years [7]. They were termed HIV controllers (HICs) or elite controllers or elite suppressors [4–7,15•, 16,17•]. Elite controllers/elite suppressor differ from traditional long-term nonprogressors (LTNPs), who maintain stable CD4 counts and are asymptomatic without antiretroviral therapy, but are usually viraemic [18]. Epidemiological studies demonstrate elite controllers represent 0.15% of HIV-infected patients [15•]. Among those, long-term elite controllers (LTECs) represent an extreme phenotype defined by virus undetectability (below the 50 copies/ml threshold) for at least 10 years with normal CD4 counts and a positive or null CD4 slope [15•]. Moreover, some studies showed that HIV-DNA levels are detectable and particularly low in peripheral blood or tissular mononuclear cells, and lower than in chronic infected patients [5,19,20]. They are thus clearly distinct from the unique case of a sterilizing functional cure described above.

Does this phenomenon result from a defective virus and/or from host's defenses? Does it reflect host's cells

resistance to efficient virus cycles or a potent immunity capable to control a viral replication? The question of the hen and the egg is however crucial in the vast majority of those elite controller studies and one should carefully distinguish the mechanisms responsible for the initiation from those involved in the maintenance of such a control while some of the observed parameters might result from the established equilibrium, as suggested by Madec *et al.* [21].

Is it the virus?

In some elite controllers, replication-competent HIV-1 cannot be isolated [22,23], but plasma virus is nevertheless detectable in the vast majority of elite controllers when using ultra-sensitive assays, and even reach higher levels than in HAART-suppressed patients [24•,25]. Detailed genotypic and phenotypic analyses strongly suggest these isolates are fully virulent [26]. According to some studies, chronic low-level viremia is suggested by discordance between the genotypes of plasma virus and of archived proviruses in resting $CD4^+$ T cells [20]. Virus sequenced from elite controller plasma and peripheral blood mononuclear cells (PBMCs) do not show consistent gene deletions or signatures that would account for a reduced replication capacity [27–31]. However, functional properties such as viral entry or virus replication capacity (VRC) in elite controllers appear to differ from chronic progressors [25,32]. Some elite controller envelope proteins show significantly decreased entry efficiency in the context of physiologic CCR5 and CD4 surface densities compared to viremic progressors, suggesting the presence of viruses with reduced entry fitness [33•]. Recombinant NL4-3 viruses encoding plasma RNA-derived *gag* or reverse *transcriptase–integrase* sequences from elite controllers displayed significantly lower VRC than those from progressors [34,35•]. Therefore, an extremely low virus replication might persist in most elite controllers in whom virus attenuation might reflect host's selective pressure.

The virus by itself does not seem to play a major role in elite control of HIV, suggesting that understanding how host factors can tame HIV is critical for a model of functional cure.

Is it the host?

The case of HIV-1 transmission from an AIDS patient to a patient who remained elite controller for 10 years [36] provided strong evidence that unique host factors explain elite control of HIV-1 replication in at least some individuals. If so, the host's mechanisms that elicit the elite controller model should provide exciting avenues of research for a functional cure.

Is it all in the genes?

Since the late 1990s, some LTNPs [37–39] and more recently elite controllers [40•] were shown to display a composite of CCR5 delta-32 gene deletion and certain class I HLA alleles that discriminate them from progressors.

The CCR5 delta-32 deletion is usually present as a heterozygous trait in approximately 30% Caucasian LTNPs or elite controllers, but still allows $CD4^+$ T cells susceptibility to HIV-1 entry and productive infection [41]. The CCR5 Delta-32 heterozygous elite controllers therefore partially share the mechanism involved in the Berlin patient.

The overrepresentation of some major histocompatibility complex (MHC) class I alleles, reported in early genetic studies using a candidate gene approach [7,37–39,42], was recently confirmed by the genome-wide association study (GWAS) approaches [40•,43]. HLA-B57, HLA-B27, and also HLA-B14 or HLA-B51 [40•] (Theodorou, unpublished observation) are the gene factors most strongly associated with protection against disease, control of virus production [40•,44], and some of them specifically controlling HIV reservoir levels [43].

What can we learn from these MHC class I associations for strategies aiming at inducing a functional cure in patients who are not blessed enough to bear these protective alleles? As MHC alleles governing immune responses the elite control of the virus appears to depend upon potent immunity to HIV. The most attenuated viruses generated from elite controller mononuclear cells come from HLA-B*57 individuals, suggesting that an early and long-term imprinting induced by the MHC-class-I-restricted immune responses on the elite controller viruses might help select viral variants and mimic the VRC reductions observed on antiretroviral drug selection pressure. Importantly some elite controllers have none of these protective alleles, while HLA-B57 does not fully protect against disease evolution. These host alleles are thus keys but neither necessary nor sufficient for elite control of viral replication. Other host gene polymorphisms might be at play and involve intracellular host defenses [43].

Role of immune defenses in elite controllers?

The predominant linkage between the MHC class I locus and HICs or elite controllers indicates that an adaptive, MHC-class-I-restricted CD8 cell-mediated control [7,45,46,47•] is involved. Strong CD8 T-cell responses to HIV-Gag are usually reported in elite controllers with various characteristics of multifunctional memory T cells producing IFN-g and IL-2, cytolytic granules [48], CD27

cell surface expression ensuring long-term survival [47•], or high functional avidity [45,49•]. Beyond these properties, those CD8 T cells display a remarkable antiviral capacity to inhibit virus production from elite controller super-infected CD4 T cells [46,48]. Continued viral suppression in HLA-B*57$^+$ individuals probably reflects strong CTL responses against unmutated and mutated epitopes [20]. To reproduce this, extraordinary control therapeutic strategies aiming at establishing a functional cure would have to augment the CD8 cell responses to HIV to the levels observed in elite controllers and use therapeutic vaccines, despite the latter did not show yet a potent ability to control the virus [50]. In addition, the abundant, multifunctional, highly avid and long-lived helper CD4 T cells specific for HIV [7,51•] help maintain robust CD8 T cells responses to HIV. These polyfunctional Gag-specific CD4$^+$ and CD8$^+$ T cells are also more abundant in mucosa from HIV controllers than in individuals on HAART, suggesting that the CD4$^+$ T-cell 'help' may be key in maintaining strong CD8$^+$ T-cell responses in the gut of HIV controllers [52]. A substantial proportion of elite controllers do not display, however, intense cell-mediated immunity to HIV, which can even be almost undetectable [7,53] suggesting other mechanisms of virus suppression are involved. Although HIV-specific T cells were not described in the single functional cure reported above, one can hypothesize that in both situations a prolonged extinction of the virus production would be accompanied by low levels of virus-specific T cells. If verified, this hypothesis would suggest that elite controller controlling the virus without robust CD8 T-cell responses might be even closer to this concept of a 'functional cure'.

Strikingly, neutralizing antibodies are almost absent in elite controllers [54–56] and even correlate positively with the viral loads in viremic LTNPs [57,58], although antibodies against all HIV proteins are still detectable. Some apparently broadly neutralizing antibodies can occasionally be detected in elite controllers but are in fact an addition of antibodies, each with a narrow spectrum [59,60]. Therefore, although one cannot definitively exclude antibodies could have contributed in the initial control of virus production in elite controllers, the persistent HIV control does not appear to be mediated by a robust humoral response. These observations are consistent with the immunologic consensus that high levels of antibodies reflect sustained virus replication, while virus extinction results in clonal contraction of activated plasmablast cells and in decay of antibody production. This situation, close to the low HIV-specific CD8 T cells observed in rare elite controllers, is similar to the Berlin patient observation of low envelope-specific antibodies.

The adaptive anti-HIV CD8 T cells might not be the only immune force driving virus control in HLA-B*57$^+$ individuals and an innate immunity mechanism mediated by natural killer (NK) cells is suggested by the strong association of the KIR3DL1 allele in those individuals [61–63]. In the contrary, antibodies to HIV-gp41 appear to block in LTNPs the NK cell pathogenic effect exerted in their absence onto CD4 T cells [64].

What about the virus reservoirs in elite controllers?

So far, little attention has been paid to the HIV reservoirs under conditions of spontaneous virus control as observed in elite controllers. HIV/SIV reservoirs are concentrated in the highly heterogeneous population of CD4 T cells and, to a much lesser degree, in monocytes/macrophages, while mostly localized in lymphoid tissues, particularly in mucosal tissues [65,66]. Cell HIV-DNA level in PBMCs is nevertheless representative of tissue infection levels [67]. Some LTNPs have been included in this study and they had particularly low levels of cell HIV-DNA levels in PBMCs and in rectum [67]. The blood cell HIV-DNA is predictive of disease evolution [19,21].

A long-term equilibrium appears to be established between virus reservoirs, virus production, and host immunity in elite controllers. HIV reservoirs, as assessed by blood cell associated HIV-DNA (cell HIV-DNA), are extremely low in elite controllers [18,21,58] and significantly associated with HLA-B57 [43] and with MHC-class-I-restricted HIV-Gag specific CD8 T cells [18,45,47•]. For some authors, the rare evolution of proviral gag sequences from HLA-B57/5801 and HLA-B27 elite suppressors suggests that ongoing replication in those elite suppressors does not permit a significant reseeding of the latent reservoir, as reported above [20]. The distribution of the very low HIV reservoir within the elite controller CD4 cell subpopulations seems to be influenced, nevertheless, by immune genes and responses, while the reservoir distribution of elite controllers who do not bear those HLA mimics the situation of treated aviremic patients in whom HIV-DNA is concentrated in the two major memory subsets, the T_{CM} and transitional memory cells (T_{TM}) (Descours and Avettand-Fenoel, unpublished observation) [68]. Thus, the influence of the HLA-B27 or HLA-B57-restricted gag-specific CD8 T cells on the HIV reservoir distribution is consistent with the concept of a low ongoing replication ensuring constant reseeding of the reservoirs in these elite controllers.

Does the immune system remain unaltered in elite controllers as participating to the functional cure?

Some immune abnormalities are observed in a substantial proportion, 10–25% of elite controllers [15•,24•]. A

progressive CD4 cell quantitative defect can even reach levels below 200 cells/μl and cause emergence of AIDS-related opportunistic events, such as pneumocystis pneumonia or Kaposi sarcomas, even in the absence of detectable plasma HIV [7,24•,69]. This CD4 deficiency is usually associated with higher levels of immune activation than in healthy uninfected controls or even in HAART-suppressed patients, which may cause atherosclerosis and cardiovascular morbidity [7,69]. Antiretroviral therapy has even been proposed in these individuals to try restoring immune competence and decreasing immune activation, although preliminary reports suggest these objectives might not be easily attainable in those peculiar elite controllers [70,71]. These immune alterations suggest that at least some elite controllers might not represent the definitive model of a functional cure.

Conclusion

Are some elite controllers a model for a functional cure? The so-called long-term elite controllers who maintain both virus undetectability and normal CD4 counts for at least 10 years appear to represent a very promising model. In the majority of those cases, a peculiar host's genetic profile induces strong antiviral cell-mediated immunity, which imprints the HIV reservoir by preserving the long-lived CD4 T cells.

How can therapeutic strategies reproduce this privileged status in the patients who are not blessed enough to bear those genetic polymorphisms? Will immune interventions reinforcing cell-mediated immunity or replacing the virus receptors on CD4 T cells be required or can other nonimmune therapeutic options reach this status? Do very early HAART interventions permit to create a protective equilibrium, at least in some patients [14]. Innovative programs will tell us whether the long-term elite control model holds its promises.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 229).

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