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REVIEW

The implications of viral reservoirs on the elite control of HIV-1 infection

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Abstract The mechanisms by which a small percentage of HIV-1 infected individuals known as elite suppressors or controllers are able to control viral replication are not fully understood. Early cases of viremic control were attributed to infection with defective virus, but subsequent work has demonstrated that infection with a defective virus is not the exclusive cause of control. Replication-competent virus has been isolated from patients who control viral replication, and studies have demonstrated that evolution occurs in plasma virus but not in virus isolates from the latent reservoir. Additionally, transmission pair studies have demonstrated that patients infected with similar viruses can have dramatically different outcomes of infection. An increased understanding of the viral factors associated with control is important to understand the interplay between viral replication and host control, and has implications for the design of an effective therapeutic vaccine that can lead to a functional cure of HIV-1 infection.

Keywords Viral fitness · Latency · Residual viremia · Elite suppression · Viral factors of control · Viral escape

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Introduction

Typically, Human Immunodeficiency Virus-1 (HIV-1) infection is characterized by very high viral loads in acute infection. During the chronic phase of infection, HIV-1 replication continues, concurrent with a progressive decline in $CD4^+$ T cells counts. Without treatment, chronic progressors (CP) will typically progress to AIDS within 5–10 years. The patients who are placed on an effective antiretroviral therapy (ART) regimen, however, will experience an increase in $CD4^+$ T cell levels and a reduction in the HIV-1 plasma RNA level, usually to undetectable levels (<50 copies/mL).

Long-term nonprogressors (LTNPs) are a subset of HIV-1 infected patients who maintain stable $CD4^+$ T cells counts greater than 500 cells/μL for longer than 7 years, in the absence of ART. Once ultrasensitive assays to detect the HIV-1 plasma RNA levels were developed, it became clear that LTNPs were a phenotypically diverse population comprised of individuals with varying HIV-1 plasma RNA levels. Elite controllers (EC) or suppressors (ES) are distinct from LTNPs in that they are defined by the level of HIV-1 RNA plasma levels rather than their $CD4^+$ T cell counts. These remarkable individuals maintain HIV-1 plasma RNA levels below the limit of detection of standard commercial assays (<50 copies/mL) in the absence of ART, and represent less than 1 % of the total HIV-1 infected population [1].

It is now generally accepted that host factors play a major role in elite control. The HLA-B*57 and B*27 alleles are over represented in EC [2–8], and these two alleles along with a polymorphism in the promoter of HLA-C have been associated with slow progression in multiple GWAS studies [9–14]. HLA class I proteins are involved in presentation of peptides to $CD8^+$ T cells, and

this may explain why HIV-specific $CD8^+$ T cells from EC are more effective at controlling HIV-1 replication in vitro than $CD8^+$ T cells from patients with progressive disease [2, 15–18]. These data complement studies in the SIV model of elite control where depletion of $CD8^+$ T cells in EC monkeys results in virologic breakthrough [19, 20].

The role of other host factors in elite control is more controversial. EC do not have elevated titers of neutralizing antibodies to autologous virus [21], but while one study suggested that these patients may have higher levels of antibody-dependant cell-mediated cytotoxicity (ADCC) than CP [22], a recent study found no differences in ADCC levels between EC and patients with progressive disease [23]. Similarly, while some studies have suggested that $CD4^+$ T cells from EC may be less susceptible to HIV-1 infection [24, 25], other studies have shown that $CD4^+$ T cells from many EC are fully susceptible to infection [26–28].

The viral factors that are associated with elite control are poorly understood. Initial reports suggested that EC were infected with defective virus, including viruses that harbored large deletions or difficult to revert polymorphisms. However, many of these studies looked at sequence analysis of proviral genes alone, and so the effect that these mutations or deletions had on the overall viral fitness was unclear [29–38]. Additionally, it was not clear whether the observed replication defects were due to infection with a defective virus, or whether the reduction in fitness was a result of a highly active immune response in patients that controlled viral replication. Using chimerical virus systems, individual HIV-1 viral genes were cloned from patients and the genes isolated from EC were seen to be less fit compared to those from CP [29, 34, 39]. Subsequently, replication-competent virus was successfully isolated from EC, indicating that some EC were, in fact, infected with virus that replicated effectively in vitro [26, 40, 41]. Full genome sequence analysis also indicated that the replication-competent virus isolated from some patients contained no large-scale deletions or gross mutations [40], and transmission pair studies have demonstrated that infection with genetically similar, replication-competent viruses can result in drastically different clinical outcomes of infection [42, 43]. The data indicate that infection with defective virus is not the exclusive cause of elite control and that some EC are infected with virus that is able to cause pathogenic disease in vivo. This has been shown definitively in the macaque model of elite control [44], where some monkeys control fully pathogenic laboratory SIV isolates through $CD8^+$ T cell responses [19, 20].

Here, we will discuss key viral factors that are associated with the control of HIV-1 viral replication in LTNPs and EC. We will focus on the fitness of the infecting virus (summarized in Table 1), latency, and residual viremia, and the implications these factors have on the host response to infection. Additionally, we will review the understanding of latency and residual viremia in EC. An increased understanding of the viral factors of elite control has important implications about the nature of the host control

Table 1 Implication of viral fitness on EC: historically, a defective infecting virus was hypothesized to result in control of viral replication, but more recent studies have suggested that, in some EC, viral fitness was not the determining factor in control. A summary of previously reported studies that summarize the debate about the fitness of the infecting virus in EC are shown, and the implication of the studies are presented

Viral characteristic	Evidence	Implications
Defective virus	Blood transfusion transmission of HIV-1 in the Sydney Blood Bank Cohort: common deletion in *nef*, no AIDS-defining symptoms [2]	Infection with a defective virus can increase the likelihood of control of HIV-1 infection
	Mutation in *nef* in a majority of 5 LTNPs studied [10]	
	Asymptomatic LTNP, infected for 20 years with a virus with a defect in *nef* [9]	
	Rare, difficult to revert polymorphism in LTNPs identified by sequence analysis [3]	
	Reduced replication capacity of chimeric *rev*, *vif*, and *gag-pol*, RT-integrase from EC [2, 7, 12]	
Attenuated virus	Escape mutations and drug resistance mutations frequently seen in plasma in primary infection in patients who controlled viral replication [21]	Attenuated virus may either be the cause or a consequence of host immune pressure in EC
	Plasma *Gag* clones in EC found to be less fit than *gag* clones from CP [11]; plasma *Env* clones from EC less efficient at entry than *Env* clones from CP [48]	
	Escape mutants found in the plasma but not significantly represented in the proviral compartment [23]	
Replication-competent virus	Detection of HIV-1 or HIV-1 protein products when $CD4^+$ T cells from EC were stimulated [13–15]	Some EC are able to suppress fully pathogenic HIV-1
	Transmission pair studies indicate viral fitness is not a determining factors for control of HIV-1 replication [16, 17]	

of replication, the design of a therapeutic vaccine, and the development of effective eradication strategies.

Viral fitness: cause or effect of elite control?

Initially, it was believed that LTNPs were infected with a defective viral strain. The earliest evidence to support this hypothesis was described in the Sydney Blood Bank Cohort. In this cohort, 7 patients were infected via blood transfusion-transmission of HIV-1 from a single infected blood donor. All patients were observed to have no decline in $CD4^+$ T cells counts and none had classical, AIDS-defining symptoms. Full genome sequencing was performed on viruses that were isolated from each patient, and a large deletion in *nef* and the U3 region of the long terminal repeat was identified in the viruses from all the patients [32]. *nef* has been shown to be important for HIV-1 replication in vitro and was shown to be required for progression in SIV monkey models of disease [35]. Subsequently, various studies identified defects in *nef* and other HIV-1 genes from EC and LTNPs [36, 37]. In one study, mutations in *nef* were identified in the majority of the five LTNPs that were studied [37]. Another case study also documented an LTNP who has been asymptomatic for 20 years and harbored a virus with a large deletion in *nef* [36]. These studies and others provide evidence for the importance of *nef* in HIV-1 pathogenesis and clearly indicate that deletions in *nef* can increase the likelihood for elite control.

Mutations and defects in other genes have also been implicated in control of HIV-1. In one such study, rare, difficult to revert polymorphisms in key genes were hypothesized to result in control of HIV-1 replication [30]. Furthermore, chimeric viruses containing *rev*, *gag-pol*, and *vif* genes from EC viral isolates were observed to have a reduced replication capacity compared to similar viruses with viral genes isolated from CPs [29, 34, 39]. More recently, it was demonstrated that some EC/viremic controllers (VC) were infected with virus containing drug resistance mutations and/or escape mutations implying that patients were more likely to control viral infection if they were infected with an attenuated viral variant [45].

These data suggest that infection with defective virus, due to mutations or deletions in key genes, can increase the likelihood of elite control. However, studies that have sequenced proviral genes from EC have reached different conclusions. In a cohort of 95 EC, plasma and proviral clones were amplified from a majority of the patients, and a high incidence of drug resistance mutations was not reported [46]. In other studies, escape mutations were rarely seen in proviral *gag* [47] and *nef* [48] clones. Furthermore, another study demonstrated that the presence of escape mutations could not explain control in patients with low level viremia [49]. Therefore, while, in some cases, infection with attenuated isolates can lead to control of HIV-1 replication, it appears that this is not the cause of elite control in many patients.

More recently, studies have suggested that some EC are not infected with defective virus. Using a highly sensitive, limiting dilution co-culture assay, replication-competent virus was isolated from a cohort of EC. These viral isolates were shown to replicate as well as laboratory X4 and R5 benchmark replication strains [40]. This study demonstrated, for the first time, that some EC were infected with full replication-competent virus. Full genome sequence analysis identified no deletions or mutations that were associated with elite control [40]. In another study, replication-competent virus was isolated from EC $CD4^+$ T cells after mitogen or IL-7 stimulation and subsequent sequence analysis indicated no deletions or insertions in the *vpr, vpu*, or *nef* genes [41]. A recent study demonstrated that stimulation of $CD4^+$ T cells from EC rarely resulted in viral outgrowth, but viral outgrowth was robust in many cases were it occurred. Viral outgrowth was more commonly observed in ART-treated patients and CP when compared to EC [26], which is consistent with studies showing that the frequency of infected $CD4^+$ T cells was much lower than the frequency usually seen in CP [40].

Most convincingly, studies that analyzed HIV-1 transmission pairs have supported the hypothesis that, in some cases, host factors predominately dictate control of viral replication [42, 43]. In these transmission pair studies, individuals were observed to transmit highly similar viruses to their partner, yet each patient had strikingly different clinical outcomes of infection. In a transmission pair study that analyzed two HLA-B*57 positive patients, fitness of the virus isolated from the EC was observed to be reduced compared to the isolates from the CP transmission partner. While the reduction in fitness was hypothesized to be a result of escape mutations that had an attenuating effect on viral fitness [42], it was also possible that the virus transmitted to the EC contained the T242N escape mutation that has previously been reported to result in a reduction in viral fitness [50, 51]. Infection with this attenuated isolate may have contributed to elite control. However, in two other cases where virus was transmitted between a patient who controlled viral replication and a CP, viral fitness was observed to be the same between all patients [43]. Thus, deficiencies in viral replication were not the root cause of control of viral replication in these cases. This suggests that fully replication-competent virus can sometimes be controlled by the immune system, and, in some cases, selective pressure from HIV-specific $CD8^+$ T cells forces and maintains attenuating escape mutations that may be playing a significant role in the control of infection.

Latency, residual viremia, and evolution in elite controllers

As a consequence of the normal physiology of $CD4^+$ T cells, latency is established early in viral infection. These latently infected cells represent a major barrier to eradication in HIV-1 infected individuals using current strategies for treatment of infection [52]. A limiting dilution, co-culture assay that approximates the number of infectious, resting $CD4^+$ T cells in a patient likely reflects the most accurate measure to quantify latently infected cells [53]. Using this assay, EC were observed to have a one and a half log lower median infectious units per millions cells (IUPM) compared to CP [40]. EC have been shown to have significantly lower levels of integrated proviral DNA [54] compared to CPs, and a recent study that looked at four unique EC with weakly reactive western blots, found that these patients had markedly lower levels of total and integrated proviral DNA compared to conventional EC. These data suggest that the control of HIV-1 replication varies between EC [55]. One study used a transcription-mediated amplification assay to assess cell-associated RNA in PBMCs and found detectable levels of RNA in 25 out 29 EC. This suggests that some level of HIV-1 transcription may be occurring in EC [56]. The reduction in the frequency of resting $CD4^+$ T cells in EC may be a result of lower levels of HIV-1 RNA during the acute phase of infection [57, 58], which could limit the seeding of the latent reservoir (Fig. 1).

Several studies have used highly sensitive RT-PCR assays to quantify the level of HIV-1 RNA in the plasma of CP and EC. While EC are typically thought to have undetectable levels of HIV-1 plasma RNA, the use of single copy assays to quantify down to 1 copy of HIV-1 RNA per mL of plasma has allowed a better understanding of the level of residual viremia in these patients. Incredibly, in multiple studies, EC were seen to have levels of virus in the plasma that were equal to those seen in ART-treated individuals [2, 56, 59, 60]. Remarkably, a significant number of patients had less than 1 copy of HIV-1 RNA per mL of plasma. An analysis of the residual viremia in EC can provide information about the nature of elite control and the effect that immune pressure has on the virus. In comparison to ART-treated patients, who were not observed have ongoing rounds of replication in multiple phylogenetic studies [61, 62], evidence for ongoing replication has been documented in EC [63–65]. Using a highly sensitive RT-PCR-based assay, O'Connell and colleagues amplified and sequenced *gag* clones from the proviral and plasma compartments at multiple time points. After phylogenetic analysis, a clear discordance between the plasma and proviral sequences was observed (representative data in Fig. 2) [64]. All the plasma sequences were observed to have mutations in HLA-B*57 restricted epitopes, whereas these escape mutations were rarely observed in the proviral compartment. Additionally, the proviral sequences were

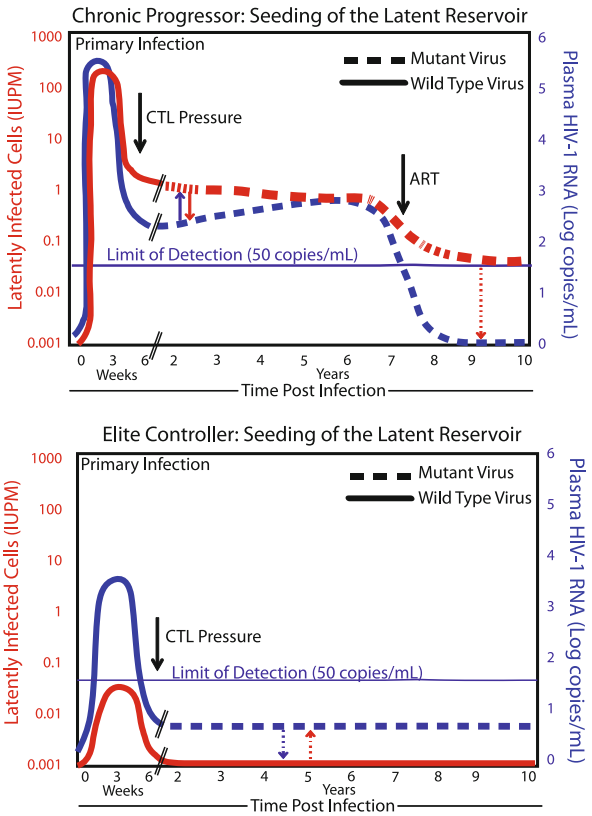

Fig. 1 Models to explain the seeding of the latent reservoir: comparison between EC and CP. *Top panel* CP natural history: HIV-1 infection is typical characterized by robust viral replication during acute infection. As HIV-1 plasma RNA levels increase (*blue line*), there is a parallel increase in the number of latently infected cells (infectious units per million, IUPM; *red line*). A drop in both the HIV-1 plasma RNA levels and IUPM occurs with the initiation of the acquired immune response, likely due to CTL pressure. Without ART, viral replication continues, and escape mutations occur early (*dotted red* and *blue lines*). High levels of replication result in an equilibrium between seeding of the latent reservoir and reactivation of the latent reservoir (*red* and *blue solid arrows*), thus resulting in the reseeding of the latent reservoir with mutated virus. Upon the initiation of ART therapy, HIV-1 plasma RNA levels fall to undetectable levels, in concert with a decline in IUPM. ART halts ongoing replication, but reactivation of the latent reservoir results in the release of low levels of virus with escape mutations (*red dashed arrow*). *Bottom panel* EC natural history. During acute infection, HIV-1 plasma RNA level increases, but has been documented to be lower in EC compared to CP (*blue line*). The frequency of latently infected $CD4^+$ T cells increases in parallel, but to levels that are lower compared to CP (*red line*). CTL pressure reduced viral replication to below the limit of detection, and there is limited seeding of the latent reservoir, resulting in a reduced IUPM in EC compared to CP. Escape occurs early in infection in EC, but there is limited seeding of the latent reservoir due to CTL pressure (*blue dashed arrow*). The majority of sequences in the latent reservoir do not contain escape mutations, as the seeding of the latent reservoir is limited by CTL pressure

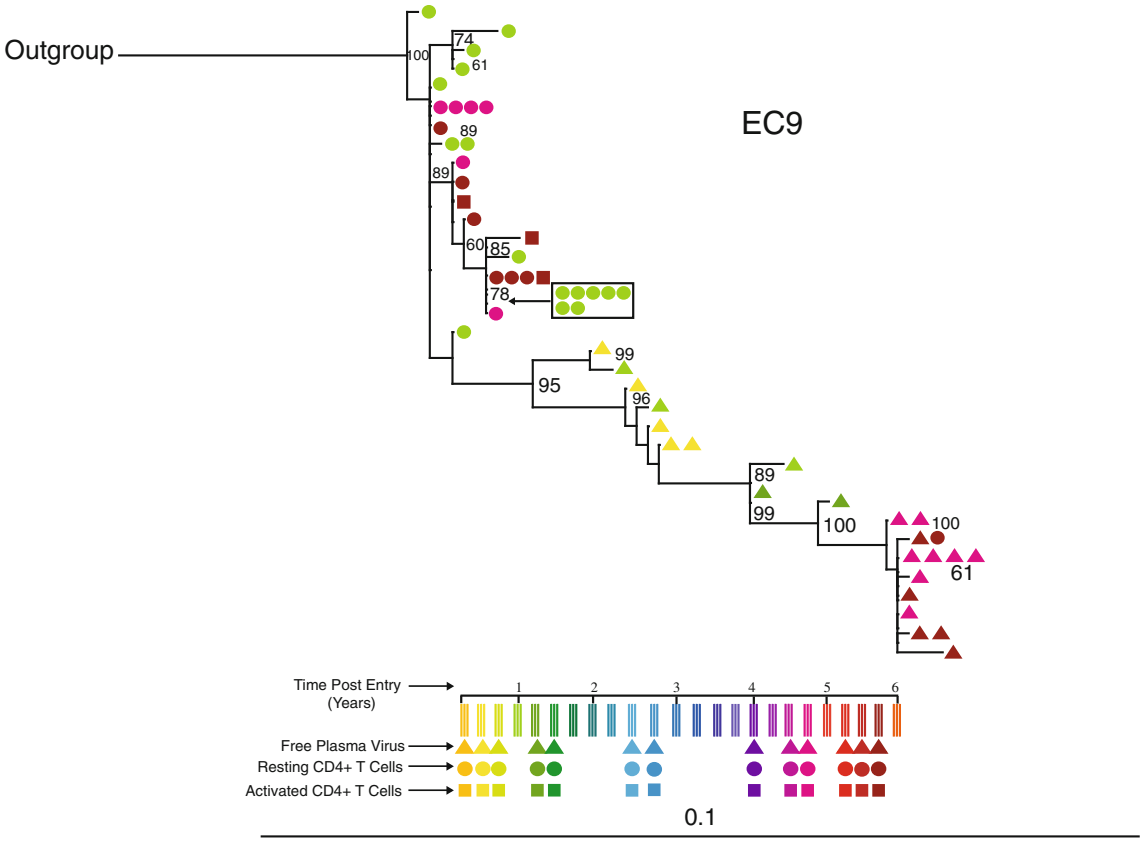

Fig. 2 Discordance between plasma and proviral sequences: evidence for ongoing replication in EC. Representative phylogenetic data from an EC demonstrating the discordance between plasma and proviral sequences as identified by limiting dilution PCR to obtain clonal *gag* sequences. All sequences were estimated using a classical approach using the maximum likelihood analysis. Clonal sequences from resting $CD4^+$ T cells, activated $CD4^+$ T cells, and plasma sequences were amplified [64]. A clear discordance between the proviral compartments in resting $CD4^+$ T cells (*circles*) and activated $CD4^+$ T cells (*squares*) can be observed compared to the plasma viral sequences (*triangles*) over a period of 6 years. The proviral compartment cluster together, with the plasma virions showing evidence of ongoing replication

ancestral to the plasma sequences. While there was evidence of synonymous evolution of clones that were amplified from the plasma, there was no evidence of evolution in the proviral *gag* clones that were amplified from resting $CD4^+$ T cells. [64]. This argues that, while ongoing viral replication occurs in the compartment that produces the low levels of virus present in the plasma, the plasma virions are not reseeding the latent reservoir of EC to a significant degree (Fig. 1).

Similar results were obtained in both a companion study that focused on analyzing the evolution of the *nef* gene [65] and a study that analyzed the evolution of clonal sequences of *RT-pol* and *env* genes from EC [63]. Interestingly, viral evolution was observed in patients with and without previously described protective HLA alleles, and evolution was found to be significantly lower in EC compared to CPs who were not on ART [63]. In the context of low level ongoing viral replication, the fact that synonymous changes were commonly observed over time in the plasma virus suggests that the virus achieved an optimal balance between immune evasion and fitness [63, 64, 66]. The discordance between escape mutations in the plasma virus in comparison to the proviral clones suggests that many EC are infected with virus that contains a wild-type sequence in many epitopes, and this virus seeds the latent reservoir early in infection. Selective pressure from CTL results in the development of escape mutations, but this occurs when the viral load is too low to lead to efficient entry into the latent reservoir. While there is minimal ongoing replication in the latent reservoir, there are probably other compartments where low level viral replication occurs. The source of this ongoing replication is unknown, but a recent study demonstrated that monocytes are not an important reservoir in EC [67].

The level of viral replication in EC is much lower than the levels seen in viremic CPs. Therefore, the virus in EC does not evolve to achieve similar levels of fitness in EC. This is best illustrated by a longitudinal study of viral fitness in HLA-B*57 LTNPs and CPs. Shortly after infection, virus isolated from PBMCs in both groups of patients had

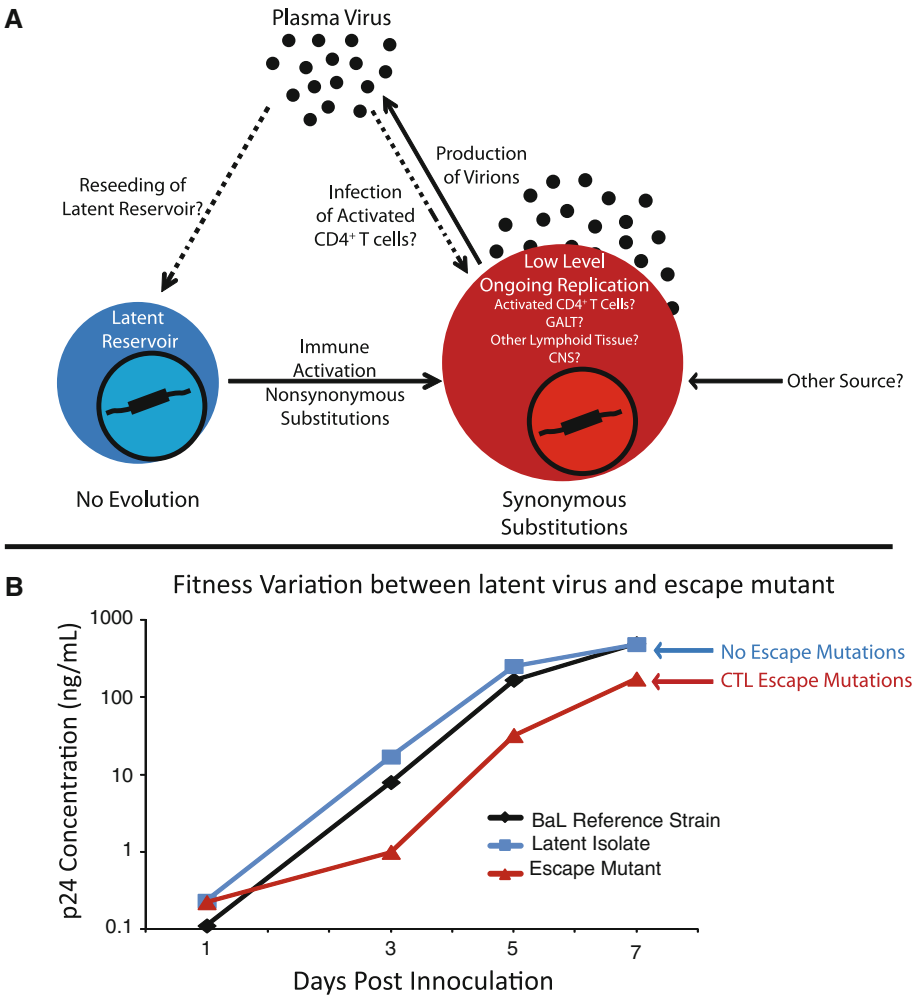

Fig. 3 Understanding the relationship between the latent reservoir and the plasma virus in EC. **a** The latent reservoir represents a major barrier to eradication, and resting $CD4^+$ T cells remain in a resting quiescent state. Integrated provirus remains silenced by poorly understood mechanisms, but minimal evolution occurs within this compartment. Upon immune activation, virus is released from these latently infected cells, and nonsynonymous mutations likely result in virions that escape immune pressure. Continuous, ongoing replication occurs in EC, the location of the replication is unknown but may be represented by either activated $CD4^+$ T cells, the gut-associated lymphoid tissue or other lymphoid organs, or the central nervous system. Plasma virions with escape mutations are not commonly represented in the latent reservoir, thus the source of these viruses are currently unknown. It has been shown that evolution occurs during low level ongoing replication, but is most commonly characterized by synonymous changes. The production of virus from this unknown compartment results in low level viremia that may re-infect the latent reservoir at very low levels or contribute to ongoing replication. **b** Representative data showing that there are clear differences in fitness between isolates cultured from resting $CD4^+$ T cells containing wild type sequence and escape mutants cultured from activated $CD4^+$ T cells [71]. Primary $CD4^+$ T cells were infected, and viral production was measured by p24 ELISA. These data indicate that the latent virus (*blue*) is more fit compared to the escape mutant (*red line*), likely due to the attenuating effect of the escape mutations. Thus, it is likely that plasma virions that contain similar escape mutations do not accurately reflect the fitness of the infecting virus that is archived in the latent reservoir

attenuating escape mutations that were present in *gag* and resulted in low viral fitness. While this low fitness virus was maintained during chronic infection in LTNPs, the fitness of the virus increased significantly over time in CPs. These data could explain why plasma *gag* clones from HLA-B*57 CPs are more likely to contain compensatory, fitness-restoring mutations compared to *gag* clones amplified from HLA-B*57 EC [68]. Thus, the maintenance of attenuating mutations that have a significant reduction in viral fitness early in infection coupled with the lack of compensatory mutations due to limited viral evolution may partially explain the control of viral replication in EC. However, unlike viremic LTNPs and CPs, HLA-B*57 EC also maintain virus that does not contain attenuating escape mutations in the latent reservoir. Thus, EC maintain control over two distinct types of virus; replication-competent

wild-type virus that is archived in a low frequency of latently infected $CD4^+$ T cells, and attenuated escape mutants that can be found at very low levels in plasma.

These attenuated plasma virions in EC have been analyzed in several studies where either the *RT-pol* [69], *gag* [38, 45] or *env* clones [70] from EC were isolated and cloned into an NL4-3 backbone. The relative replicative capacity of these clones was found to significantly lower than chimeric clones from CPs. Attenuating mutations were correlated with protective HLA epitopes [69].

These studies are limited by the fact that they look only at single viral genes in isolation. Thus, compensatory or detrimental mutations elsewhere in the genome are unaccounted for, and complete viral variants are not compared. More importantly, plasma viruses are subject to selective pressure and may not be representative of the original infecting virus. Mutations in plasma viruses in *gag* [47], *nef* [48], and *env* [21] have been identified that are very rare in the $CD4^+$ T cell proviral compartment. For example, the attenuating T242N mutation was found in almost all plasma sequences from EC, but was not equally reflected in the proviral compartment [47]. A similar discordance was observed in *nef* in another study [48]. Most convincingly, in a recent study, replication-competent virus was isolated from activated and resting $CD4^+$ T cells. The isolate from the activated $CD4^+$ T cells resembled plasma virus and contained multiple escape mutations in *gag*. In contrast, the virus cultured from resting $CD4^+$ T cells resembled proviral clones and did not contain escape mutations. In a fitness assay, the virus containing the escape mutants was significantly less fit than a reference laboratory strain, whereas the archived virus from resting $CD4^+$ T cells had no evidence of attenuation (Fig. 3) [71]. These data indicate that the virus that this patient was infected with did not possess escape mutations or viral attenuation, instead these mutations were acquired over time as a result of selective pressure exerted by HIV-specific CTL. Therefore, while informative, the analysis of plasma clones alone may not provide conclusive evidence to support or refute the relationship between viral fitness and elite control, and nor do they represent an accurate representation of the original infecting virus. Studies looking at replication-competent virus isolated from resting $CD4^+$ T cells are needed for this purpose.

Concluding remarks

An increased understanding of the viral factors that influence elite control is still necessary to provide information on the nature and mechanisms of control of HIV-1 replication. While it is clear that, in some cases, EC are infected with defective viral strains, there is abundant evidence to suggest that this is not the sole explanation for elite control. Infection with an attenuated virus can increase the likelihood of control of viral replication, but it is probable that, in some cases, a combination of host and viral factors are required to fully suppress viral replication and, in others, host factors alone lead to the control of fully pathogenic virus. Comparing EC with chronically infected and ART-treated patients is informative, but it is clear that differences in the levels of viral replication early in infection may result in irrevocable alteration in both the host response to viral infection and the replicative capacity of the infecting virus. Thus, comparisons made between these patient populations are imperfect and must reflect these limitations. It is clear that the analysis of plasma virions and relying on sequence analysis alone are not sufficient. The isolation and amplification of replication-competent viruses from EC is paramount in furthering our understanding of viral factors of control.

Ultimately, EC represent a unique model system where the host immune response to HIV-1 infection can be studied. This is not a perfect model for control of HIV-1 replication since, in some cases, immune activation [72, 73], declining $CD4^+$ T cells counts [59, 72–75], and spontaneous virologic breakthrough [76] have been reported; however, it appears that the majority of EC have maintained stable $CD4^+$ T cell counts and control of viral replication for more than 20 years. Because of the inability of the host response to eliminate latently infected HIV-1 cells, EC can and should be used as model system for a functional cure where the latent reservoir is contained rather than eradicated. Additionally, because it has been shown that some, if not a majority, of EC are infected with fully replication-competent virus, the study of host factors and their contributions toward an effective immune response can lead to the development of novel strategies for an effective HIV-1 therapeutic vaccine.

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