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HIV-1 replicative fitness in elite controllers

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Abstract

Purpose of review—Differential rates of disease progression are obviously multifactorial, but the virulence of the actual infecting virus is most frequently ignored as potential source of slow or rapid disease progression. In this review, the argument will be made that nearly all elite suppressors are infected by weak HIV-1 strain (in terms of replicative capacity). Whether this poor virus replication is the cause of elite suppression or the consequence of a strong immune response remains a leading question in the field.

Recent findings—Although numerous research studies have related HIV-1 replicative capacity/fitness in tissue culture to virulence within patients, this review will focus on several recent and key discoveries on the important role of HIV-1 fitness in elite suppression. First, elite suppressors appear to harbor HIV-1 variants that encode Gag, Pol, and Env proteins that are less efficient than their counterparts of HIV-1 in typical/chronic progressors. Second, the actual HIV-1 clone(s) that establish acute infection may be less fit in patients who become elite controllers as compared with typical progressors. Finally, the fitness costs of cytotoxic T lymphocyte escape in HIV-1 may be easily compensated by secondary mutations if the infecting strain is capable of high replication kinetics and rapid evolution. A strain with weak replicative capacity might not compensate for fitness loss or even generate the initial escape mutations.

Summary—A combination of good, anti-HIV-1 host genetics (e.g. HLA-B*57) along with infection by a ‘whimpy’ HIV-1 strain may be necessary for elite suppression, whereas only one of these may lead to slow progression and viremia.

Keywords

cytotoxic T lymphocyte escape; elite controllers; HIV-1 fitness; HLA alleles

Introduction

A small percentage of the HIV-infected population maintain viral loads that are low enough to be undetectable by conventional clinical assays (<50 copies viral RNA per ml blood) and experience a protracted course of HIV-1 infection with slow or minimal progression to AIDS. These rare HIV-infected individuals are frequently referred to as elite controllers because of this dramatic and spontaneous control of viremia. The molecular mechanisms underlying elite control are an area of active research. Rigorous molecular studies indicate that at least the majority of these individuals experience a persistent low level of viremia suggesting that there is some degree of ongoing viral replication [1–4]. Several recent studies have suggested that the phenotype of the infecting virus may play a role in this elite control. This review discusses the potential contribution of viral fitness to elite control of HIV-1 viremia.

Impact of drug resistance and immune escape on HIV-1 replicative fitness

Multiple exogenous factors can impact the overall replicative fitness of an HIV-1 isolate and contribute to viral pathogenesis *in vivo* [5–12]. Selective pressures on HIV-1, such as extrinsic drug treatment and intrinsic immune response, can select for resistance mutations that negatively impact viral replicative fitness.

Among drug resistance mutations, the M184V mutation in reverse transcriptase has been most consistently associated with a significant loss in replicative fitness [13,14]. The *in-vivo* impact of the M184V mutation was further evaluated in a large-scale clinical study of HIV-infected antiviral naïve patients. Those patients infected with viruses containing the M184V mutation had significantly lower viral loads relative to patients without this mutation [15]. These clinical data suggest that specific drug resistance mutations can significantly affect viral load independent of other host factors.

Mutations caused by pressure from the human immune system can similarly have dramatic effects on viral replication capacity. The degree of replication impairment caused by these changes is variable and is often associated with the properties of the viral gene. The relative effects of the cellular and humoral immune responses have been the subject of significant investigation. Recent studies noted minimal to absent fitness impact by the humoral and cellular immune response to the envelope protein (Env) [16,17*] and much more dramatic fitness costs by the cellular immune response targeting conserved structural motifs [17*,18–20]. The high degree of natural sequence variation in the *env* gene results in a highly plastic molecule that can tolerate a large number of mutations without any detectable change in activity. Mutations in structural proteins like those in reverse transcriptase or Gag result in more dramatic changes in activity. Consequently, cytotoxic T lymphocyte (CTL) escape mutations typically incur a larger fitness cost in Gag molecules than in Env molecules [17*].

It has been widely demonstrated that variations in the consensus Gag sequence caused by escape from CTL-mediated immune pressures result in fitness costs to HIV-1 replication. While CTL escape mutations do have discernable fitness impacts *in vitro*, these mutations also directly correlate to lower viral load *in vivo*. In a large cross-sectional study of Zambian

transmission pairs, HLA class I-restricted escape mutations in *gag* and *nef* were readily transmitted to recipient partners. Transmission of viral variants with a greater number of CTL escape mutations correlated with lower viral loads in the newly infected partner [21]. This study suggests that transmission of viruses with reduced fitness resulting from CTL escape mutations independently contributes to lower viral load set point.

Fitness of viral isolates from elite controllers

Although long-term nonprogression has been associated with reduced replication capacity of viral quasiespecies [22], few studies have directly evaluated the fitness of viral isolates derived directly from elite controllers. Low levels of proviral DNA in elite controllers have made it difficult to recover full-length replication competent virus from these individuals [2]. Two laboratories have successfully propagated replication competent virus from a small number of patients using modified pooled donor, co-culture outgrowth assays. Blankson *et al.* [23] recovered viral clones from 4/10 elite controllers, and Julg *et al.* [24] recovered clones from 2/14 elite controllers. Many factors may contribute to the low success rate of viral recovery aside from low viral levels, including slow replication kinetics of proviral clones, the presence of defective viruses, and other host cellular factors. These clonal viruses exhibited no gross deletions or absent gene products. Viral replication was readily detected in cell lines [24] and phytohemagglutinin/interleukin-2-activated peripheral blood mononuclear cells from heterologous [23,24] and autologous [23] donors. Monoculture exponential growth assays demonstrated a lack of gross replicative defects in these viruses. Taken together, these data from outgrowth assays suggest that elite controllers harbor viruses that are replication competent without gross ‘attenuating’ fitness defects. These data were supported in a third study demonstrating outgrowth of replication competent viruses from both viremic and aviremic controllers [25]. It should be noted, however, that these assays potentially favor outgrowth of high replicative fitness variants, and low replicative fitness variants may not be successfully recovered at such low titers. Further, quantitative assessment of viral replication capacity is limited in the logarithmic monoculture assays used to study these viruses to date, making it difficult to assess the presence of more subtle fitness differences [7,26,27].

Consistent with this data, high throughput sequencing of peripheral blood-derived viral genomes similarly demonstrated a lack of gross genetic defects [28]. More rigorous fitness studies have been conducted on isolated HIV-1 gene products using chimeric viruses containing gene segments from elite controllers’ peripheral blood-derived viruses. This dataset strongly highlighted the interplay of CTL escape and viral fitness costs. Analysis of fitness associated with the TW10 epitope located in Gag from 50B*57/B5801⁺ elite controllers carrying the canonical T242N escape mutation exhibited reduced replication capacity [29]. Furthermore, other unique mutations flanking this epitope were found in the elite controllers population that were further associated with a more profound fitness defect. Interestingly, these unique variants elicited strong interferon- γ responses suggesting these epitopes are targeted *in vivo* providing some evidence for the contribution of both viral fitness defects and a robust immune response in elite control.

The replicative capacity of elite controller virus was further evaluated in another study by cloning plasma-derived *gag* genes from 54 elite controllers and 41 chronic progressors into a laboratory viral strain (NL4-3) and then comparing replication rates [30^{**}]. A significant reduction in relative replication capacity of the elite controller-derived viruses over the chronic progressor-derived viruses was found. Although this difference was statistically significant, there was a great deal of overlap between the relative fitness of individual elite controller-derived viruses relative to chronic progressor-derived viruses. A similar reduction in replication capacity was observed for plasma-derived elite controllers *reverse transcriptase-integrase* genes compared with these chronic progressor-derived gene products when cloned into NL4-3 [31]. These findings suggest that the *gag* and *pol* genes may contribute to a reduced replicative fitness, but there was no evidence of highly defective viruses in these elite controller patients [30^{**},31].

The large number of elite controllers in this cohort study allowed for evaluations of subtle fitness effects as well as subgroup analysis by human leukocyte antigen (HLA) haplotype [30^{**},31]. This analysis revealed that HLA haplotype alone was strongly associated with viral fitness independent of controller or noncontroller status. B*57-positive elite controllers harbored HIV-1 with *gag* genes that contributed to lower fitness values than other elite controllers with non-B*57 alleles, and similarly B*57-positive chronic progressor harbored *gag* genes that contributed to fitness values lower than non-B*57 alleles. This strong correlation between host HLA status and viral fitness indicated that viruses replicating in the face of a robust CTL responses may carry CTL escape mutations (at least in the *gag* gene) that exert a fitness cost [30^{**},31]. Potentially, a targeted CTL response can force outgrowth of a population of moderately attenuated virus and this in turn lowers viral load. Taken together, these data suggest a role for *gag* gene fitness in elite control; however, the observed fitness costs alone are not sufficient to explain control.

Chimeric virus technology has also been used to evaluate plasma-derived Env proteins from elite controllers. Lassen *et al.* [32^{**}] compared a population of *env* clones from seven elite controller and seven chronic progressor patients and also found a significantly lower fitness values in the elite controller-derived virus versus chronic progressor-derived virus based on the *env* gene. This differentiation was evident when *env*-chimeric viruses were evaluated as individual clones and when pooled to approximate the patient's quasispecies. Functional analysis of these envelopes demonstrated significant reductions in affinity for both of the primary host cell receptors CD4 and CCR5 with elite controller-derived viruses, and that this impaired affinity led to reduced rates of virus entry. The smaller number of patients in this study did not permit subgroup evaluation to stratify viral fitness based on HLA haplotype. It remains unclear whether CTL pressure could result in decreased fitness in Env, or alternatively if this fitness deficit in Env is a stochastic result of a transmission bottleneck.

Impaired viral fitness in elite controllers: cause or consequence

The identification and characterization of low fitness viral variants in elite controllers created a plausible assumption that the enrichment of protective HLA alleles (e.g. B*57 and B*27) resulted in rapid immune escape and that these escape mutations come with higher fitness costs [30^{**},32^{**}]. In support of this hypothesis, several studies suggest that escape

mutations in B*57-restricted and B*27-restricted epitopes may have higher fitness costs than possible escape variants in other epitopes restricted by other class I alleles [20,33,34]. Most studies on elite controllers involve samples collected years after identification of disease status. Thus, it is assumed that a virus with wild-type levels of replicative fitness established infection and that the low fitness state was derived from a strong cell-mediated host immune response. The alternative to this assumption is also possible. Elite controllers may be infected initially with low-fitness HIV-1 variants which never establish progressive infection. Low viral loads in HIV-1 infections can be correlated to low replicative fitness and slow rates of HIV-1 evolution, as assessed by both divergence from the infecting virus clone and the diversity of the HIV-1 population at a given time point [7,35]. Inpatient HIV-1 population diversities in elite controllers are much lower than in chronic progressors, and yet the emergence of CTL escape mutations is evident in both patient populations [36,37]. Differences may relate to compensatory mutations emerging more rapidly and frequently in chronic progressors than in elite controllers.

Many questions remain regarding controller status with regards to protective HLA alleles. Why do some HIV-infected B*27 and B*57 patients experience typical progression? Why do half of elite controllers lack a protective HLA allele? Clearly other host genetic or environmental factors may contribute to elite controller status. Another possible factor may be the fitness of the infecting virus. CTL escape leaves a genetic footprint in all coding sequence of HIV-1 and at least in the *gag* gene, these initial escape variants are of lower fitness [7,20,33]. However, CTL escape mutations in the HIV-1 *env* gene have minimal impact on replicative fitness and in some instances, actually increase replication capacity. Troyer *et al.* found that fitness neutral mutations were observed in all CTL escape epitopes that emerged during the first 1000 days of infection and as early as 50 days after infection. In other studies, it has been reported that the fitness of the HIV-1 *env* genes increases during disease progression [7,38]. The consequence of this increase being that replicative fitness of the entire virus is significantly impacted by the *env* gene and relates to efficiency of host cell entry [27,39]. The most accurate estimate of in-vivo replicative fitness is likely obtained from assessment of the entire HIV-1 isolate. An ideal but challenging assessment of the impact of replicative fitness on subsequent disease progression would entail measuring replicative capacity of full-length viruses derived from acute infection and then followed serially through time.

Figure 1 is a theoretical model for the various categories of disease progression with contributions from host immune background and HIV-1 viral fitness: typical or chronic progressors (~90% of infections), rapid progressors (~5%), slow progressors (~5%), and elite controllers (<1%). The combination of strong protective host genetics and infection with an HIV-1 clone of poor fitness from the donor population could lead to elite control of viremia. Protective host genetics or infection with a virus with low replicative fitness alone might lead to slower progression. Finally, rapid progression may be the result of poor host genetics (e.g. B*35) or neutral genetics in combination with infection of a highly virulent HIV-1 clone from the donor HIV-1 population.

Transmission of lower fitness variants

Transmission of viruses containing fitness defects has been an area of active research. Comparison of elite controller-derived and chronic progressor-derived Env clones to clones derived from a cohort at acute infection showed that there was broad overlap in function among the acute infection Env proteins with both elite controllers and chronic progressor viruses [32^{**}]. This finding was surprising given the recent data suggesting that, typically, only a single variant from a complex quasispecies ultimately will become the founder virus [40]. Based on these data, it is generally assumed that the virus with the highest replicative fitness from that donor quasispecies is the virus to successfully found a new infection. This observed variability in the fitness of acute infection viral clones suggested the possibility that elite controllers are initially infected with a viral variant with reduced replicative fitness, possibly offering a ‘priming’ period for the host immune system to effectively suppress viral replication [32^{**}].

To further address this question, a longitudinal study of individuals enrolled at acute infection identified several individuals who went on to become viremic controllers (viral load <2000) or elite controllers [41^{**}]. Elite controllers had lower average peak viral loads at acute infection. *Gag-pro* chimeric viruses demonstrated significantly lower fitness of the infecting virus in individuals who went on to become controllers than in those who failed to control infection. In this cohort, there was no enrichment of protective HLA alleles found in those who went on to control viremia, although interestingly there was a high frequency of founder viruses containing prototypical Gag CTL escape mutations associated with escape from known protective alleles. Founder viruses in controllers also contained a significant increase in the frequency of drug resistance mutations. Interestingly, this increased frequency of drug resistance mutations was not noted in a large-scale study of viruses present in elite controllers during the chronic phase of infection suggesting these mutations may be lost over time [28]. Taken together, these data suggest that early events in HIV-1 primary infection mediated by replicative fitness of the founder virus itself may have a significant durable effect on outcome in long-term infection.

This model is also supported by a single transmission pair study by Bailey *et al.* [42]. This group evaluated viral quasispecies in an individual who developed AIDS and who was the transmission donor to a recipient who became an elite controller. Both individuals harbored Gag variants with T242N mutation. The progressor additionally carried compensatory mutations that restored wild-type fitness to the Gag molecule. Evaluation of the relative fitness of these genes indicated that the virus found predominantly in the elite controllers exhibited significantly lower fitness [42]. In this patient, it was impossible to determine whether transmission of a low fitness variant to the recipient (subsequently an elite controller) allowed for less immunodepletion fueling a robust immune response or if the immune response alone was sufficient to suppress evolution of low fitness variants. Regardless, these data suggest that maintenance of HIV-1 variants with low replicative fitness contributes to overall control of viremia.

Superinfection and escape from control

Loss of viral suppression in elite controllers has been documented on rare occasions, and has been associated both with changes in the primary infecting virus as well as superinfection with a novel heterologous virus.

Longitudinal analysis of an HLA-B*57-positive patient who controlled viremia shortly after seroconversion demonstrates the multifactorial nature of viral control, and is suggestive of the subtle role of viral fitness [43]. The patient was an elite controller for more than a year, but then lost the ability to control viremia. Loss of viral control in this patient was associated with contemporaneous mutations in two HLA-B*57-restricted epitopes in Gag, as well as reversion of the drug resistance-associated M184V mutation. An additional mutation in Vpu, an accessory protein known to impact viral release, was also temporally associated with increases in viral load. These findings suggested that both the loss of CTL pressure combined with increased viral fitness resulted in escape from viral control in this individual.

Loss of HIV-1 viral control in the setting of superinfection has been documented on several occasions and is also indicative of the role of viral fitness in elite control. An HLA-B*57-positive elite controller experienced a super-infection event from a viremic individual who lacked protective HLA-alleles [44]. Subsequent to superinfection, the elite controllers failed to fully control the super-infecting virus to levels achieved from the initial infecting virus, as indicated by a 2 log increase in viral load. A second study describes two elite controllers who were both hospitalized with acute retroviral syndrome [45]. Genetic analysis revealed that each patient had experienced a superinfection with a phylogenetically divergent virus [45]. This data suggests that in some patients viral phenotype plays an important role in virologic outcome. Of note, superinfection of HIV-1 elite controllers may happen more frequently than is documented if the majority of superinfection events result in no change in viral load. This small case series does however give some indication that the sole presence of a robust immune system does not offer universal protection from detectable HIV-1 viremia and disease progression, and suggests that the infecting or circulating virus itself may contribute some portion of the balance in viral load setpoint.

Conclusion

Viral load setpoint appears to be a complex and multi-factorial phenotype mediated by factors derived from both the host and the virus. No single unifying mechanism has been elucidated to explain the extraordinarily low viral setpoints found in elite controllers. Viral replicative fitness can be significantly impacted by host CTL pressure, antiretroviral drugs, and by apparently stochastic changes in viral sequence. Recent studies even suggest that viral phylogeny plays an important role in defining host viral load setpoint [46]. Highly defective HIV-1 has not been isolated from elite controllers but the *gag*, *pol*, and *env* genes support less efficient HIV-1 replication when cloned into a neutral HIV-1 backbone. Thus, the collective deficiencies may result in significant decreases in replicative fitness of viruses derived from elite controllers versus chronic progressors. The cause or origin of this decreased HIV-1 fitness remains unknown, but it might be a combination of both acute infection with a low fitness virus clone and subsequent accumulation of CTL escape

mutations further reducing fitness. Deleterious CTL escape mutations in HIV-1 are more evident with patients harboring protective HLA alleles. Further studies on viral fitness in elite controllers are obviously necessary, including characterization of full-length viruses from acute infection and longitudinal time points to ascertain if escape mutations to host immune response are sufficient to drive down viral fitness to levels of avirulence.

Understanding the host mechanisms involved in manipulating viral fitness may allow for more rational design of vaccine immunogens.

Acknowledgments

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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. 230).

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Key points

- The HIV-1 *gag*, *pol*, and *env* genes of elite suppressors as compared with those of typical progressors encode viral proteins that are less efficient/fit for virus replication/production.
- An elite status of disease progression may be established at acute infection due to the infection of HIV-1 clone of poor replicative fitness.
- Cell-mediated immune response directed at HIV-1 can further decrease replicative fitness of an already weak virus by selecting for an escape mutation with a fitness cost.
- The combination of good (anti-HIV) host genetics (e.g. HLA B*57) and infection with a low fitness HIV-1 strain may set the stage for efficient control of viremia and lack of disease progression.

Figure 1.

A schematic illustration to describe a model for the rare transmission of HIV-1 clones of low fitness to various recipients with different genetics defined as ‘good’ or protective, ‘neutral’, or ‘bad’ because of the support of more rapid HIV-1 disease progression