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Understanding animal models of elite control: windows on effective immune responses against immunodeficiency viruses

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Abstract

Purpose of review—We will summarize recent advances in research regarding control of simian immunodeficiency virus (SIV) replication in non-human primate models. We will then relate these findings to the broader field of human immunodeficiency virus (HIV) vaccine development.

Recent findings—Recent studies have highlighted the importance of T cell responses in elite control, especially CD8+ T cell responses, and provide insight into the kinetics and qualities of such effective responses. Additionally, these findings suggest that the peptides bound by elite control-associated MHC class I molecules in monkeys and humans share many properties.

Summary—Animal models of effective immune control of immunodeficiency virus replication have provided important insight into the components of successful immune responses against these viruses. Similarities between the human and non-human primate responses to immunodeficiency viruses should help us understand the nature of elite control. Further study of the acute phase, where virus replication is first brought under control may help define important characteristics of viral control that could be engendered by a successful HIV vaccine.

Keywords

CD8+ T cell; elite control; animal model; immune control

Introduction

A vaccine is desperately needed to curb the still growing global HIV pandemic. Recent estimates project that for every HIV-infected individual initiating anti-retroviral treatment, more than two individuals are newly infected [1]. A vaccine that prevents virus transmission is clearly the most cost-effective way to slow such rapid growth of the pandemic. Vaccines have historically been chosen based on their ability to induce responses that mimic successful immune responses to human pathogens, yet correlates of successful immune

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responses against HIV remain an enigma. There are no reported cases of a human immune system clearing the virus after clinically detectable infection. Elite control of chronic phase viral replication, which appears in many cases to be mediated by the immune system, is the best model of an effective immune response against the virus.

Human elite control has been associated with several genetic variations. However, the most prevalent and strongest genetic association centers on the major histocompatability complex, specifically the HLA-B locus [2-4]. We have discovered an animal model of this phenomenon in Indian rhesus macaques experimentally inoculated with the highly pathogenic SIVmac239 clonal isolate [5, 6]. This animal model has several advantageous features: the sequence of the infecting virus is known and can be manipulated, the timing and route of infection can be strictly controlled, and early acute phase phenomena can be easily followed. In addition, more frequent and invasive sampling can be completed in this rhesus macaque animal model of immune control of HIV replication.

Many discoveries in animal models of HIV infection have been shown to be applicable to human pathogenesis. These include the importance of CD8+ T cell responses in acute phase viremia resolution and chronic phase viral control [7-10], the presence and functional significance of viral escape from CD8+ T cell responses [11-14] and the reversion of CD8+ T cell escape mutations *in vivo* [15-17]. The unique properties of the animal model, along with the newly discovered similarities between this model and human elite control [18*, 19*] make the SIV-infected Indian rhesus macaque ideal for discovering mechanisms of immune control that might be translatable into useful components of a vaccine to contain the HIV pandemic.

The importance of CD8+ T cells in immune control

CD8+ T cells have been known to play a role in the containment of HIV and SIV infections for quite some time, both *in vitro* [20, 21] and *in vivo* [7, 22]. The mechanism as to how these CD8+ T cells exert their antiviral effects remains unknown. Elegant studies performed concurrently by two groups [23**, 24] sought to determine whether CD8+ T cells exert their control by direct cytolytic clearance of virus-infected target cells *in vivo*. Both groups used mathematical models to determine the rates of viral decay *in vivo* in the presence or absence of CD8+ T cells in groups of animals initiating a reverse transcriptase inhibitor-based antiretroviral therapy regimen. The groups hypothesized that if CD8+ T cells kill virally infected cells directly, the rate of viral decay in animals initiating anti-retroviral therapy would be slower in animals lacking CD8+ T cells when compared to animals with an intact repertoire of lymphocytes. To their surprise, they found equivalent rates of viral decay post-antiretroviral therapy initiation in animals depleted of CD8+ T cells and in control antibody or undepleted animals. These intriguing results suggest that CD8+ T cells, while still important in maintaining control of viral replication, do not exert their control via direct killing of infected cells, rather by an indirect mechanism.

Another recently published study used a different approach to arrive at a similar conclusion [25*]. The authors studied the kinetics of immune escape using a sensitive quantitative PCR assay that can discriminate between wild-type viral quasispecies and those that contain a particular escape mutation. They reasoned that if escape were mediated by CD8+ T cell cytolysis, the death rate of wild-type virus infected cells would be faster than that of escape mutant virus infected cells *in vivo*. They found the rates were equivalent, suggesting a non-cytolytic mechanism drives escape from CD8+ T cell responses *in vivo*.

After effective control of viral replication has been established in the post-acute phase, other immune responses may develop that result in viral control. In line with this idea, a serial re-challenge experiment evaluating the capacity of CD8+ T cell escape mutant viruses to

superinfect elite controller animals revealed that these escaped viruses did not replicate in elite controller animals [26*]. Despite the well-demonstrated *in vitro* and *in vivo* fitness of the mutant escape viruses, the authors were unable to superinfect animals with viruses containing multiple known Mamu-B*17 escape mutations, the MHC class I allele associated with elite control in this model. This suggests that, despite selection of CD8+ T cell escape mutations, these viruses do not possess the capacity to overwhelm an immune system that has already brought viral replication under control. Effective CD8+ T cell responses might then play a more critical role in the initiation of immune control during acute infection and, while still important in chronic infection as demonstrated by CD8-depletion studies [10], be one piece of a larger puzzle of control maintained by many different arms of the immune system.

Work from our own lab further suggests such a critical acute phase role for CD8+ T cell responses against epitopes bound by elite control-associated MHC class I molecules [27*]. Approximately 50% of animals expressing the protective *Mamu-B*08* MHC class I allele control chronic viral replication of the highly pathogenic SIVmac239 clonal isolate after challenge. This control is likely mediated by Mamu-B*08-restricted CD8+ T cells [28, 29]. To test this hypothesis, we introduced escape mutations into eight known Mamu-B*08-restricted CD8+ T cell epitopes of SIVmac239 and infected a cohort of 10 *Mamu-B*08*+ rhesus macaques with this mutant cloned virus. Even though the virus showed no fitness defects *in vitro*, one of two *Mamu-B*08*-negative animals challenged with this mutant virus controlled chronic phase viral replication. Nevertheless, in spite of this potential fitness defect *in vivo*, the incidence of elite control in a cohort of ten *Mamu-B*08*+ animals challenged with the mutant virus (2 of 10) was significantly reduced when compared with wild-type virus infected animals (10 of 15) indicating a critical role for Mamu-B*08-restricted CD8+ T cell responses in the initiation of elite control.

Similarities between human and animal models of elite control

In the past several months, similarities between animal models of elite control and the phenomenon in humans have become clearer, emphasizing the importance of studying these models. Our own efforts to understand the Mamu-B*08 model of MHC class I-associated elite control have revealed a key similarity between Mamu-B*08 and HLA-B*2705, a human MHC class I molecule associated with elite control [19*]. Despite diverging at 28 amino acid positions in the primary sequence, these molecules share similar peptide binding motifs, including an identical position 2 arginine primary anchor and major overlaps in preferred binding residues at the other dominant position 1 and position 9 residues. Both molecules also share a preference for arginine at position 1 leading to the selection of peptides with di-basic amino termini. These types of peptides are resistant to peptidases and therefore may be more stable resulting in better MHC class I loading and presentation [30]. We also found that approximately 70% (in a panel of 899) of HLA-B*2705-binding peptides could also bind to Mamu-B*08. Therefore two MHC class I alleles associated with elite control of immunodeficiency virus replication share similar peptide binding motifs and bind many of the same peptides.

Further highlighting similarities between human and animal models of elite control, another recent study suggested that MHC class I molecules in Chimpanzees, which control viral replication and do not progress to AIDS after infection with SIVcpz or HIV-1, may target many of the same regions of the virus as HLA-B*27 and HLA-B*57 [18*]. This includes highly conserved regions of the virus, especially those in Gag which have previously been associated with elite control in HLA-B*27+ and HLA-B*57+ humans [31, 32].

Conclusion

Evidence suggests that CD8+ T cells play a key role in the control of immunodeficiency virus replication in animal models and in humans. Elite control in both humans and Indian rhesus macaques is associated with particular MHC class I alleles. Furthermore, recent focus has shifted to properties of the peptides bound by the protective alleles as playing a role in elite control [4, 19*, 33] and also the functional superiority of T cell responses restricted by protective alleles [34]. In spite of this knowledge, understanding the exact nature of this control and translating these findings into an effective HIV vaccine remains difficult. Therefore, a broader understanding of the components of the effective T cell responses in individuals who control viral replication will be needed to provide a framework for the development of vaccine strategies. These components may be as simple as the viral location of effective responses, breadth or magnitude, but may also prove more complex to translate into an effective vaccine.

Many open questions remain to be answered before knowledge of elite control mechanisms can be used to assist in the development of an HIV vaccine. The exact kinetics of effective CD8+ T cell responses remain unknown, but we presume they must be present and exerting their unique effects early in the acute phase for individuals to become elite controllers. Escape from these responses in the chronic phase of viral replication is not always associated with breakthrough in viral control [26*, 29, 32, 35, 36]. In addition, in animal models of MHC class I-associated elite control, viral loads in animals that control viral replication and those that do not begin to diverge as early as 4 weeks post-infection and significantly diverge by 8 weeks post-infection. Understanding early events in these animals will be important in deciphering the correlates of elite control.

Interestingly, not every individual with a protective MHC class I allele becomes an elite controller. Approximately 50% of *Mamu-B*08*+ animals and 20% of *Mamu-B*17*+ animals infected with SIVmac239 control viral replication. Understanding the characteristics of the CD8+ T cell responses and other potential immunological differences between individuals that control and those that do not could shed important light on the characteristics of effective anti-retroviral immune responses. Current work focuses on acute phase differences in T cell and other immune responses between individuals that control and those that do not.

The location of effective CD8+ T cell responses as well as characteristics such as cross-reactivity and clonal specificity of the responding population could prove to be key determinants of effective T cell control of immunodeficiency virus infections. Correlation of public clonotypes, markers of specific clonal populations of T cells, with viral control in a vaccine model has been demonstrated [37]. It remains to be seen if specific clonotypes of T cells are protective in natural models of immune control when comparing individuals who control with those that do not.

Natural animal models of elite control, such as the Mamu-B*08 and Mamu-B*17 models, provide a largely untapped resource for studying other aspects of the immune response in addition to CD8+ T cell responses. Investigations testing hypotheses regarding the importance of CD4+ T cells, humoral immunity and innate immunity may discover important adjuncts for effective CD8+ T cell responses that must also be elicited by a successful HIV vaccine. Previous work in our laboratory has suggested an important role for CD4+ T cells in elite control [38]. Projects exploring CD4+ T cells and other arms of the immune system in elite control are currently underway.

Animal models of immune-mediated elite control offer a unique opportunity to explore correlates of viral control. Most of the hypotheses being tested in the current models are difficult to address in research with human subjects, especially research involving the first

weeks of the acute phase of viral infection. Translating recent knowledge in our understanding of elite control into useful components of an effective HIV vaccine will require that we further define key aspects of these immune responses that can be mimicked by a vaccine.

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Key Points

1. Animal models of elite control share many properties with human elite control.
2. Animal models of elite control provide unique opportunities to study elite control, including the ability to control the sequence of the infecting virus, the timing of the infection and the ability to frequently sample various compartments during acute infection.
3. CD8+ T cells appear to play a key role in MHC class I-associated elite control in Indian rhesus macaques.