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Qualitative Features of the HIV-Specific CD8⁺ T cell Response Associated with Immunologic Control

Adam R. Hersperger², Stephen A. Migueles¹, Michael R. Betts², and Mark Connors^{1,*}

¹HIV-Specific Immunity Section, Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland ²Department of Microbiology, University of Pennsylvania, Philadelphia, Pennsylvania

Abstract

Purpose of review—Over the past 2 years a clearer picture has emerged regarding the properties of HIV-specific CD8⁺ T cells associated with immunologic control of HIV replication. These properties represent a potential mechanism by which rare patients might control HIV replication in the absence of antiretroviral therapy. This review addresses the background and recent findings that have lead to our current understanding of these mechanism(s).

Recent findings—Patients with immunologic control of HIV are not distinguished by targeted specificities, or greater numbers or breadth of their HIV-specific CD8⁺ T cell response. For this reason, recent work has focused greater attention on qualitative features of this response. The qualitative features most closely associated with immunologic control of HIV are related to the granule-exocytosis mediated elimination of HIV-infected CD4⁺ T cells. The ability of HIV-specific CD8⁺ T cells to increase their contents of proteins known to mediate cytotoxicity, such as granzyme B and perforin, appears to be a critical means by which HIV-specific cytotoxic capacity is regulated.

Summary—Investigation from multiple groups has now focused upon HIV-specific CD8⁺ T-cell granule-exocytosis mediated cytotoxicity as a correlate of immunologic control of HIV. In the near future, a more detailed understanding of the qualities associated with immunologic control may provide critical insights regarding the necessary features of a response that should be stimulated by immunotherapies or T-cell based vaccines.

Keywords

Long-term nonprogressors (LTNP); elite controllers (EC); CD8⁺ T cells; perforin; cytotoxicity

Introduction

With the availability in the late 1990's of ultrasensitive assays capable of quantifying plasma HIV RNA levels down to 50 copies/ml, it became clear that a subset of HIV-infected patients had very low levels of viral replication despite years of infection without receiving

*Corresponding author: Mark Connors, LIR, NIAID, NIH, Bldg 10, Rm 11B-09, 10 Center Dr MSC 1876, Bethesda, MD 20892-1876, Phone: 301-496-8057, Fax: 301-402-0070; mconnors@nih.gov.

antiretroviral therapy. At different medical research centers where they are followed, these patients have been variably termed long-term nonprogressors (LTNP), elite controllers (EC), elite suppressors or HIV controllers, but will be referred to as LTNP/EC for the purposes of this review (recently reviewed in [1]). The definitions of these patients have also varied among centers resulting in some differences in clinical characteristics and host genetics [1]. However, the majority of patients in these cohorts are characterized by sustained viral RNA levels below 50 copies/ml plasma in the absence of antiretroviral therapy. Over the past 15 years, the HIV-specific immune responses of these patients have been extensively studied and compared with those targeting other viruses and the HIV-specific responses of progressors. In this review, we will discuss the background that led to the current understanding that HIV-specific CD8⁺ T cell responses in these patients are primarily responsible for suppressing HIV replication over many years. We will also discuss the much clearer picture that has recently emerged regarding the mechanism(s) by which CD8⁺ T cells might mediate this effect.

Evidence for CD8⁺ T Cell Mediated Control of HIV in LTNP/EC

There are several lines of evidence suggesting that host genetics and host immune response factors, not virus factors, are responsible for controlling HIV in LTNP/EC. For example, CD4⁺ T cells from both progressors and LTNP/EC appear to support equivalent levels of viral replication [2–4]. In addition, the viruses recovered from most LTNP/EC are fully replication competent [5]. Although some minor defects in virus replication capacity have been observed, these are likely the result of immune selection pressure and not the cause of nonprogression [6–8]. In addition, there are examples of transmission to persons who became LTNP/EC of viruses that were sufficiently pathogenic to cause disease progression in the transmitter [9]. Lastly, in an SIV-infected rhesus macaque model of LTNP/EC, infection with a cloned SIVmac239 virus, that is highly pathogenic for most animals, can be controlled [10,11]. Thus, the majority of the evidence suggests that control of HIV replication in most LTNP/EC is not a result of a diminished ability of their CD4⁺ T cells to support viral replication or reduced viral replicative capacity.

The vast majority of evidence suggests that the HIV-specific CD8⁺ T-cell response mediates immunologic control in LTNP/EC. There is a dramatic overrepresentation of the HLA class I alleles B*57 and B*27 in most cohorts of LTNP/EC (reviewed in [1]). Similarly, associations between the protective MHC alleles Mamu B*08 and B*17 and nonprogressor status have been found in LTNP/EC macaques [10,11]. The importance of these associations between particular MHC alleles and immune control have been further supported by whole-genome association analyses, which have consistently revealed that the factors most strongly associated with nonprogressive HIV infection are either HLA class I alleles or single nucleotide polymorphisms that are in linkage disequilibrium with HLA B*5701 [12–15]. Additionally, the HIV-specific CD8⁺ T-cell response in B*57⁺ LTNP/EC patients is highly focused upon HIV peptides restricted by this allele, suggesting that immune-mediated control is not due to a gene in linkage disequilibrium with B*57, but rather directly involves the B57 molecule [16,17]. In addition, the LTNP/EC macaque model has provided direct evidence for the role of the CD8⁺ T-cell response in mediating immunologic control in this setting [18]. Depletion of CD8⁺ T cells by administration of an anti-CD8 monoclonal

antibody results in a loss of restriction of SIV replication in these animals. As antibody levels fall and CD8⁺ T cells rebound, immunologic control is restored [18]. Taken together, there is now a large body of evidence indicating that the CD8⁺ T-cell response is responsible for immunologic control in the vast majority of LTNP/EC.

Qualitative Features of Effective HIV-Specific CD8⁺ T Cells in LTNP/EC

Over the past decade, new tools have permitted an extensive characterization of the HIV-specific CD8⁺ T-cell response of LTNP/EC. As a result, a number of features of HIV-specific CD8⁺ T cells that might account for control of virus replication have been eliminated from the list of possibilities. There is now general agreement that LTNP/EC are not distinguished from progressors on the basis of the frequencies of HIV-specific CD8⁺ T cells in the peripheral blood (reviewed in [19])[17,20]. In addition, the CD8⁺ T-cell response of LTNP/EC is not differentiated from that of progressors on the basis of specificity or greater breadth (reviewed in [19] and [21]) [16,17,20]. Differences in functional avidity have also not been reliably observed [8,22–25]. In addition, the same escape mutations have been found at comparable frequencies within immunodominant epitopes of sequences derived from HLA-B*57⁺ LTNP/EC and progressors [5,7,8,23,25]. Furthermore, there is no difference between the CD8⁺ T cells of LTNP/EC and progressors in the ability to recognize the autologous virus [23,24]. Taken together, these observations strongly suggest that insufficient recognition of the patient's autologous virus is not the mechanism responsible for the vast differences in immunologic control between progressors and LTNP/EC. Instead, these findings suggest that qualitative features of the CD8⁺ T-cell response mediate immunologic control of HIV in LTNP/EC.

Although work since the late 1990's has continued to support that immunologic control of HIV in LTNP is due to qualitative features of the host immune response, it was also clear that these qualitative features were not being measured by even the most advanced assays. More recently, some differences in qualitative features of the HIV-specific CD8⁺ T-cell response have begun to emerge. HIV-specific CD8⁺ T cells of LTNP exhibit a greater number of functions compared to progressors in response to HIV antigens [26–28]. However, although these “polyfunctional” cells can comprise a large proportion of CD8⁺ T cell responses against other viruses such as EBV and CMV, they are a relatively small subset of HIV-specific CD8⁺ T cells [29]. Recently, the CD8⁺ T cells of LTNP/EC were found to have a much greater capacity than those of progressors to suppress HIV replication *in vitro* [30].

Association of Proliferative Capacity with Restriction of HIV Replication

Several lines of evidence have linked immunologic control of HIV with greater proliferative capacity of virus-specific CD8⁺ T cells. HIV-specific CD8⁺ T cells of LTNP/EC are distinguished from those of progressors by the maintenance of HIV-specific CD8⁺ T cells with a high proliferative capacity [22,31–33]. *In vitro*, preferential proliferation of B5701-restricted compared to non-B5701-restricted CD8⁺ T cells of LTNP/EC with this allele has also been observed [33]. Similarly, B57-restricted CD8⁺ T-cells preferentially expand *in vivo* during acute infection [34] and there is some evidence for their preferential expansion in response to HIV vaccines [35]. In addition, there is some evidence of an association

between greater control of SIV challenge viruses and the ability of SIV-specific CD8⁺ T cells to expand *in vivo* [36,37]. The importance of proliferative capacity in the control or elimination of antigen may extend beyond lentiviral infection. Proliferative capacity has been observed to be an important correlate of a successful immune response in LCMV infection of mice, hepatitis C infection in humans, and passive transfer therapy studies of melanoma in humans [38–41].

Association between Perforin Expression and Immunologic Control

The greater ability of the HIV-specific CD8⁺ T-cells of LTNP/EC to proliferate compared to progressors is paralleled by or possibly linked to the ability to increase the perforin content of cytotoxic granules. When examined directly *ex vivo*, HIV-specific CD8⁺ T cells from LTNP/EC and progressors have low or absent perforin expression [22,42–45]. However, following stimulation, the HIV-specific CD8⁺ T cells of LTNP/EC were found to greatly increase perforin expression over 3–6 days. In contrast, the HIV-specific CD8⁺ T-cells of progressors proliferate poorly and have only a limited ability to upregulate perforin over the same time.

Recent data suggests that perforin expression in virus-specific CD8⁺ T cells can be measured more rapidly after restimulation [46,47]. Although previous studies have observed increases in perforin protein only following 72 hours of stimulation and typically associated with proliferation [22,44,46–49], some data suggest that newly produced perforin mRNA and protein can be detected within hours of T cell activation [29,46,47,50–52]. HIV-specific CD8⁺ T cells from LTNP/EC display a greater ability to upregulate perforin compared to progressors after six hours of peptide stimulation [51]. Thus, together these studies indicate that EC have an enhanced ability to upregulate perforin after a brief restimulation [51] as well as after *in vitro* proliferation [22].

Association Between Cytotoxic Granule Contents and Cytotoxicity

For some time, it remained unclear whether differences between LTNP/EC and progressors in the ability to increase the contents of cytotoxic granules translated into greater cytotoxic capacity. Most HIV-specific CD8⁺ T cells isolated from the peripheral blood have very low amounts of perforin and have been observed to be poorly cytotoxic [22,42,44,53]. In addition to perforin, LTNP/EC were found to have a greater ability to upregulate granzyme B following stimulation [53]. No differences have been found, however, in the ability of cells from these two patient groups to degranulate [51,53]. Recently, using an assay designed to measure cytotoxic capacity on a per-cell basis, HIV-specific CD8⁺ T cells of LTNP were observed to mediate rapid and efficient elimination of HIV-infected CD4⁺ T cell targets via the granule exocytosis pathway in contrast to the responses observed with the cells of progressors [53]. ART did not restore cytotoxic capacity in progressors, which suggested that loss of these functions is likely not simply a consequence of high-level viremia during the chronic phase of infection [28,53]. In several studies, cytotoxic capacity has now been very strongly associated with perforin contents of HIV-specific CD8⁺ T cells [28,53,54]. Taken together, these lines of evidence suggest that an important correlate of HIV-specific CD8⁺ T cell-mediated control of viremia in LTNP/EC is the long term maintenance of perforin-mediated effector activity.

The disruption of multiple different functions of HIV-specific CD8⁺ T cells of progressors, such as proliferation and expression of cytolytic granule-associated proteins, may suggest that the underlying defect(s) in effector functionality lie in the elements controlling their expression. For example, we have recently found that HIV-specific CD8⁺ T cells from LTNP/EC express higher levels of the transcription factor T-bet compared to progressors [55]. This T-box transcription factor has previously been associated with CD8⁺ T cell effector function and differentiation in both mice and humans [29,56].

Potential Importance for Vaccines and Immunotherapies

One of the goals for the study of LTNP/EC is to provide a better understanding of the mechanisms that could be exploited in T-cell based vaccines and immunotherapies. It is not necessarily the case that control of HIV induced by a T-cell based vaccine would be mediated through similar mechanisms to those operative in LTNP/EC. However, there are some emerging data to suggest that some similarities exist. As noted above, HLA B5701-restricted cells were found to be preferentially expanded in volunteers with this allele following a canarypox-HIV recombinant vaccination [35]. Similar HLA associations were recently observed in the large efficacy trial of the Merck Ad5 trivalent vaccine or Step trial [57]. Greater CD8⁺ T cell responses to Gag were strongly associated with HLA B alleles associated with control of HIV in a genome wide association study. In a separate study of the same vaccine, greater HIV-specific CD8⁺ T-cell cytotoxic capacity was observed in samples from patients with these same protective B alleles [58]. Taken together, it appears that similarities exist between observations in chronic infection and vaccination. However, because vaccines for HIV thus far have not induced a response that lowers viral load after infection, the predictive value of inducing a strong cytotoxic response cannot be assessed at this time. In addition, the precise mechanism by which a greater response is induced in patients with protective alleles remains incompletely understood.

Summary

Considerable progress has been made over the past decade in understanding the mechanism(s) by which LTNP/EC might control HIV replication. In the last few years, a series of observations has come from several different labs that has resulted in a more cohesive paradigm for understanding immunologic control. Greater ability of the cells of LTNP/EC compared to those of progressors to increase their cytotoxic granule contents and, thereby, increase their cytotoxic capacity appear to be the HIV-specific CD8⁺ T cell functions that are most clearly associated with immunologic restriction of HIV replication. Parallel observations in vaccinees underscore the potential implications of these observations for T-cell based vaccines for HIV.

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References

1. Migueles SA, Connors M. Long-term nonprogressive disease among untreated HIV-infected individuals: clinical implications of understanding immune control of HIV. *JAMA*. 2010; 304:194–201. [PubMed: 20628133]
2. Lopez Bernaldo de Quiros JC, Shupert WL, McNeil AC, Gea-Banacloche JC, Flanigan M, Savage A, Martino L, Weiskopf EE, Immamichi H, Zhang YM, et al. Resistance to Replication of HIV Challenge Virus in SCID-Hu Mice Engrafted with PBMC of Nonprogressors is Mediated by CD8+ T cells and Associated with a Proliferative Response to p24 Antigen. *Journal of Virology*. 2000; 74:2023–2028. [PubMed: 10644376]
3. Rabi SA, O'Connell KA, Nikolaeva D, Bailey JR, Jilek BL, Shen L, Page KR, Siliciano RF, Blankson JN. Unstimulated Primary CD4+ T Cells from HIV Type 1 Positive Elite Suppressors are Fully Susceptible to HIV-1 Entry and Productive Infection. *J Virol*. 2010
4. Julg B, Pereyra F, Buzon MJ, Piechocka-Trocha A, Clark MJ, Baker BM, Lian J, Miura T, Martinez-Picado J, Addo MM, et al. Infrequent recovery of HIV from but robust exogenous infection of activated CD4(+) T cells in HIV elite controllers. *Clin Infect Dis*. 2010; 51:233–238. [PubMed: 20550452]
5. Blankson JN, Bailey JR, Thayil S, Yang HC, Lassen K, Lai J, Gandhi SK, Siliciano JD, Williams TM, Siliciano RF. Isolation and characterization of replication-competent human immunodeficiency virus type 1 from a subset of elite suppressors. *J Virol*. 2007; 81:2508–2518. [PubMed: 17151109]
6. Brockman MA, Schneidewind A, Lahaie M, Schmidt A, Miura T, Desouza I, Ryvkin F, Derdeyn CA, Allen S, Hunter E, et al. Escape and compensation from early HLA-B57-mediated cytotoxic T-lymphocyte pressure on human immunodeficiency virus type 1 Gag alter capsid interactions with cyclophilin A. *J Virol*. 2007; 81:12608–12618. [PubMed: 17728232]
7. Navis M, Schellens I, van Baarle D, Borghans J, van Swieten P, Miedema F, Kootstra N, Schuitemaker H. Viral replication capacity as a correlate of HLA B57/B5801-associated nonprogressive HIV-1 infection. *J Immunol*. 2007; 179:3133–3143. [PubMed: 17709528]
8. Miura T, Brockman MA, Schneidewind A, Lobritz M, Pereyra F, Rathod A, Block BL, Brumme ZL, Brumme CJ, Baker B, et al. HLA-B57/B*5801 human immunodeficiency virus type 1 elite controllers select for rare gag variants associated with reduced viral replication capacity and strong cytotoxic T-lymphocyte recognition. *J Virol*. 2009; 83:2743–2755. [PubMed: 19116253]
9. Bailey JR, O'Connell K, Yang HC, Han Y, Xu J, Jilek B, Williams TM, Ray SC, Siliciano RF, Blankson JN. Transmission of human immunodeficiency virus type 1 from a patient who developed AIDS to an elite suppressor. *J Virol*. 2008; 82:7395–7410. [PubMed: 18495769]
10. Yant LJ, Friedrich TC, Johnson RC, May GE, Maness NJ, Enz AM, Lifson JD, O'Connor DH, Carrington M, Watkins DI. The high-frequency major histocompatibility complex class I allele Mamu-B*17 is associated with control of simian immunodeficiency virus SIVmac239 replication. *J Virol*. 2006; 80:5074–5077. [PubMed: 16641299]
11. Loffredo JT, Maxwell J, Qi Y, Glidden CE, Borchardt GJ, Soma T, Bean AT, Beal DR, Wilson NA, Rehauer WM, et al. Mamu-B*08-positive macaques control simian immunodeficiency virus replication. *J Virol*. 2007; 81:8827–8832. [PubMed: 17537848]
12. Fellay J, Shianna KV, Ge D, Colombo S, Ledergerber B, Weale M, Zhang K, Gumbs C, Castagna A, Cossarizza A, et al. A whole-genome association study of major determinants for host control of HIV-1. *Science*. 2007; 317:944–947. [PubMed: 17641165]
13. Catano G, Kulkarni H, He W, Marconi VC, Agan BK, Landrum M, Anderson S, Delmar J, Telles V, Song L, et al. HIV-1 disease-influencing effects associated with ZNRD1, HCP5 and HLA-C alleles are attributable mainly to either HLA-A10 or HLA-B*57 alleles. *PLoS ONE*. 2008; 3:e3636. [PubMed: 18982067]
14. Dalmaso C, Carpentier W, Meyer L, Rouzioux C, Goujard C, Chaix ML, Lambotte O, Avettand-Fenoel V, Le Clerc S, de Senneville LD, et al. Distinct genetic loci control plasma HIV-RNA and cellular HIV-DNA levels in HIV-1 infection: the ANRS Genome Wide Association 01 study. *PLoS ONE*. 2008; 3:e3907. [PubMed: 19107206]
15. The Major Genetic Determinants of HIV-1 Control Affect HLA Class I Peptide Presentation. *Science*. 2010

16. Goulder PJ, Bunce M, Krausa P, McIntyre K, Crowley S, Morgan B, Edwards A, Giangrande P, Phillips RE, McMichael AJ. Novel, cross-restricted, conserved, and immunodominant cytotoxic T lymphocyte epitopes in slow progressors in HIV type 1 infection. *AIDS Res Hum Retroviruses*. 1996; 12:1691–1698. [PubMed: 8959245]
17. Migueles SA, Sabbaghian MS, Shupert WL, Bettinotti MP, Marincola FM, Martino L, Hallahan CW, Selig SM, Schwartz D, Sullivan J, et al. HLA B*5701 is highly associated with restriction of virus replication in a subgroup of HIV-infected long term nonprogressors. *Proc Natl Acad Sci U S A*. 2000; 97:2709–2714. [PubMed: 10694578]
18. Friedrich TC, Valentine LE, Yant LJ, Rakasz EG, Piaskowski SM, Furlott JR, Weisgrau KL, Burwitz B, May GE, Leon EJ, et al. Subdominant CD8+ T-cell responses are involved in durable control of AIDS virus replication. *J Virol*. 2007; 81:3465–3476. [PubMed: 17251286]
19. Migueles SA, Tilton JC, Connors M. Advances in understanding immunologic control of HIV infection. *Curr HIV/AIDS Rep*. 2004; 1:12–17. [PubMed: 16091218]
20. Betts MR, Ambrozak DR, Douek DC, Bonhoeffer S, Brenchley JM, Casazza JP, Koup RA, Picker LJ. Analysis of total human immunodeficiency virus (HIV)-specific CD4(+) and CD8(+) T-cell responses: relationship to viral load in untreated HIV infection. *J Virol*. 2001; 75:11983–11991. [PubMed: 11711588]
21. Migueles SA, Tilton JC, Connors M. Qualitative host factors associated with immunological control of HIV infection by CD8 T cells. *Curr Opin HIV AIDS*. 2006; 1:28–33. [PubMed: 19372780]
22. Migueles SA, Laborico AC, Shupert WL, Sabbaghian MS, Rabin R, Hallahan CW, Van Baarle D, Kostense S, Miedema F, McLaughlin M, et al. HIV-specific CD8+ T cell proliferation is coupled to perforin expression and is maintained in nonprogressors. *Nat Immunol*. 2002; 3:1061–1068. [PubMed: 12368910]
23. Migueles SA, Laborico AC, Imamichi H, Shupert WL, Royce C, McLaughlin M, Ehler L, Metcalf J, Liu S, Hallahan CW, et al. The differential ability of HLA B*5701+ long-term nonprogressors and progressors to restrict human immunodeficiency virus replication is not caused by loss of recognition of autologous viral gag sequences. *J Virol*. 2003; 77:6889–6898. [PubMed: 12768008]
24. Draenert R, Verrill CL, Tang Y, Allen TM, Wurcel AG, Boczanowski M, Lechner A, Kim AY, Suscovich T, Brown NV, et al. Persistent recognition of autologous virus by high-avidity CD8 T cells in chronic, progressive human immunodeficiency virus type 1 infection. *J Virol*. 2004; 78:630–641. [PubMed: 14694094]
25. Bailey JR, Williams TM, Siliciano RF, Blankson JN. Maintenance of viral suppression in HIV-1-infected HLA-B*57+ elite suppressors despite CTL escape mutations. *J Exp Med*. 2006; 203:1357–1369. [PubMed: 16682496]
26. Betts MR, Nason MC, West SM, De Rosa SC, Migueles SA, Abraham J, Lederman MM, Benito JM, Goepfert PA, Connors M, et al. HIV nonprogressors preferentially maintain highly functional HIV-specific CD8+ T cells. *Blood*. 2006; 107:4781–4789. [PubMed: 16467198]
27. Zimmerli SC, Harari A, Cellerai C, Vallerian F, Bart PA, Pantaleo G. HIV-1-specific IFN-gamma/IL-2-secreting CD8 T cells support CD4-independent proliferation of HIV-1-specific CD8 T cells. *Proc Natl Acad Sci U S A*. 2005; 102:7239–7244. [PubMed: 15872023]
28. Migueles SA, Weeks KA, Nou E, Berkley AM, Rood JE, Osborne CM, Hallahan CW, Coglianor-Shutta NA, Metcalf JA, McLaughlin M, et al. Defective human immunodeficiency virus-specific CD8+ T-cell polyfunctionality, proliferation, and cytotoxicity are not restored by antiretroviral therapy. *J Virol*. 2009; 83:11876–11889. [PubMed: 19726501]
29. Makedonas G, Hutnick N, Haney D, Amick AC, Gardner J, Cosma G, Hersperger AR, Dolfi D, Wherry EJ, Ferrari G, et al. Perforin and IL-2 upregulation define qualitative differences among highly functional virus-specific human CD8 T cells. *PLoS Pathog*. 2010; 6:e1000798. [PubMed: 20221423]
30. Saez-Cirion A, Lacabartz C, Lambotte O, Vermisse P, Urrutia A, Boufassa F, Barre-Sinoussi F, Delfraissy J-F, Sinet M, Pancino G, et al. HIV controllers exhibit potent CD8 T cell capacity to suppress HIV infection ex vivo and peculiar cytotoxic T lymphocyte activation phenotype. *Proc Natl Acad Sci USA*. 2007; 104:6776–6781. [PubMed: 17428922]
31. Lichterfeld M, Kaufmann DE, Yu XG, Mui SK, Addo MM, Johnston MN, Cohen D, Robbins GK, Pae E, Alter G, et al. Loss of HIV-1-specific CD8+ T cell proliferation after acute HIV-1 infection

- and restoration by vaccine-induced HIV-1-specific CD4+ T cells. *J Exp Med.* 2004; 200:701–712. [PubMed: 15381726]
32. Arrode G, Finke JS, Zebroski H, Siegal FP, Steinman RM. CD8+ T cells from most HIV-1-infected patients, even when challenged with mature dendritic cells, lack functional recall memory to HIV gag but not other viruses. *Eur J Immunol.* 2005; 35:159–170. [PubMed: 15580653]
 33. Horton H, Frank I, Baydo R, Jalbert E, Penn J, Wilson S, McNevin JP, McSweyn MD, Lee D, Huang Y, et al. Preservation of T cell proliferation restricted by protective HLA alleles is critical for immune control of HIV-1 infection. *J Immunol.* 2006; 177:7406–7415. [PubMed: 17082660]
 34. Altfeld M, Addo MM, Rosenberg ES, Hecht FM, Lee PK, Vogel M, Yu XG, Draenert R, Johnston MN, Strick D, et al. Influence of HLA-B57 on clinical presentation and viral control during acute HIV-1 infection. *Aids.* 2003; 17:2581–2591. [PubMed: 14685052]
 35. Kaslow RA, Rivers C, Tang J, Bender TJ, Goepfert PA, El Habib R, Weinhold K, Mulligan MJ. Polymorphisms in HLA class I genes associated with both favorable prognosis of human immunodeficiency virus (HIV) type 1 infection and positive cytotoxic T-lymphocyte responses to ALVAC-HIV recombinant canarypox vaccines. *J Virol.* 2001; 75:8681–8689. [PubMed: 11507213]
 36. Hel Z, Venzon D, Poudyal M, Tsai WP, Giuliani L, Woodward R, Chougnet C, Shearer G, Altman JD, Watkins D, et al. Viremia control following antiretroviral treatment and therapeutic immunization during primary SIV251 infection of macaques. *Nat Med.* 2000; 6:1140–1146. [PubMed: 11017146]
 - 37•. Hansen SG, Vieville C, Whizin N, Coyne-Johnson L, Siess DC, Drummond DD, Legasse AW, Axthelm MK, Oswald K, Trubey CM, et al. Effector memory T cell responses are associated with protection of rhesus monkeys from mucosal simian immunodeficiency virus challenge. *Nat Med.* 2009; 15:293–299. This study, which has important implications for HIV vaccine design, showed that long-term CD8-mediated protection from repeated intrarectal challenge with SIV can be successfully induced in rhesus macaques vaccinated with chronically replicating rhesus cytomegalovirus vectors expressing SIV gene products. [PubMed: 19219024]
 38. Wedemeyer H, He XS, Nascimbeni M, Davis AR, Greenberg HB, Hoofnagle JH, Liang TJ, Alter H, Rehermann B. Impaired effector function of hepatitis C virus-specific CD8+ T cells in chronic hepatitis C virus infection. *J Immunol.* 2002; 169:3447–3458. [PubMed: 12218168]
 39. Wherry EJ, Teichgraber V, Becker TC, Masopust D, Kaech SM, Antia R, von Andrian UH, Ahmed R. Lineage relationship and protective immunity of memory CD8 T cell subsets. *Nat Immunol.* 2003; 4:225–234. [PubMed: 12563257]
 40. Wherry EJ, Blattman JN, Ahmed R. Low CD8 T-cell proliferative potential and high viral load limit the effectiveness of therapeutic vaccination. *J Virol.* 2005; 79:8960–8968. [PubMed: 15994790]
 41. Rosenberg SA, Dudley ME. Adoptive cell therapy for the treatment of patients with metastatic melanoma. *Curr Opin Immunol.* 2009; 21:233–240. [PubMed: 19304471]
 42. Appay V, Nixon DF, Donahoe SM, Gillespie GM, Dong T, King A, Ogg GS, Spiegel HM, Conlon C, Spina CA, et al. HIV-specific CD8(+) T cells produce antiviral cytokines but are impaired in cytolytic function. *J Exp Med.* 2000; 192:63–76. [PubMed: 10880527]
 43. Lieberman J, Shankar P, Manjunath N, Andersson J. Dressed to kill? A review of why antiviral CD8 T lymphocytes fail to prevent progressive immunodeficiency in HIV-1 infection. *Blood.* 2001; 98:1667–1677. [PubMed: 11535496]
 44. Zhang D, Shankar P, Xu Z, Harnisch B, Chen G, Lange C, Lee SJ, Valdez H, Lederman MM, Lieberman J. Most antiviral CD8 T cells during chronic viral infection do not express high levels of perforin and are not directly cytotoxic. *Blood.* 2003; 101:226–235. [PubMed: 12393740]
 45. Appay V, Dunbar PR, Callan M, Klenerman P, Gillespie GM, Papagno L, Ogg GS, King A, Lechner F, Spina CA, et al. Memory CD8+ T cells vary in differentiation phenotype in different persistent virus infections. *Nat Med.* 2002; 8:379–385. [PubMed: 11927944]
 46. Hersperger AR, Makedonas G, Betts MR. Flow cytometric detection of perforin upregulation in human CD8 T cells. *Cytometry A.* 2008; 73:1050–1057. [PubMed: 18615597]

47. Lu P, Garcia-Sanz JA, Lichtenheld MG, Podack ER. Perforin expression in human peripheral blood mononuclear cells. Definition of an IL-2-independent pathway of perforin induction in CD8+ T cells. *J Immunol.* 1992; 148:3354–3360. [PubMed: 1588036]
48. Meng Y, Harlin H, O’Keefe JP, Gajewski TF. Induction of cytotoxic granules in human memory CD8+ T cell subsets requires cell cycle progression. *J Immunol.* 2006; 177:1981–1987. [PubMed: 16849512]
49. Sandberg JK, Fast NM, Nixon DF. Functional heterogeneity of cytokines and cytolytic effector molecules in human CD8+ T lymphocytes. *J Immunol.* 2001; 167:181–187. [PubMed: 11418647]
50. Makedonas G, Banerjee PP, Pandey R, Hersperger AR, Sanborn KB, Hardy GA, Orange JS, Betts MR. Rapid up-regulation and granule-independent transport of perforin to the immunological synapse define a novel mechanism of antigen-specific CD8+ T cell cytotoxic activity. *J Immunol.* 2009; 182:5560–5569. [PubMed: 19380804]
51. Hersperger AR, Pereyra F, Nason M, Demers K, Sheth P, Shin LY, Kovacs CM, Rodriguez B, Sieg SF, Teixeira-Johnson L, et al. Perforin expression directly ex vivo by HIV-specific CD8 T-cells is a correlate of HIV elite control. *PLoS Pathog.* 2010; 6:e1000917. This study provided direct ex vivo evidence that HIV-specific CD8+ T cells from LTNP/EC are capable of immediate production of perforin after activation, providing an additional effector mechanism of control in HIV elite controllers. [PubMed: 20523897]
52. Celleraï C, Perreau M, Rozot V, Enders FB, Pantaleo G, Harari A. Proliferation capacity and cytotoxic activity are mediated by functionally and phenotypically distinct virus-specific CD8 T cells defined by interleukin-7R{alpha} (CD127) and perforin expression. *J Virol.* 2010; 84:3868–3878. [PubMed: 20130059]
53. Migueles SA, Osborne CM, Royce C, Compton AA, Joshi RP, Weeks KA, Rood JE, Berkley AM, Sacha JB, Cogliano-Shutta NA, et al. Lytic granule loading of CD8+ T cells is required for HIV-infected cell elimination associated with immune control. *Immunity.* 2008; 29:1009–1021. [PubMed: 19062316]
54. Harari A, Enders FB, Celleraï C, Bart PA, Pantaleo G. Distinct profiles of cytotoxic granules in memory CD8 T cells correlate with function, differentiation stage, and antigen exposure. *J Virol.* 2009; 83:2862–2871. This study is a systematic examination of the cytotoxic granule contents and related functions of virus-specific CD8+ T-cells. [PubMed: 19176626]
55. Hersperger A, Martin J, Shin L, Sheth P, Kovacs C, Cosma G, Makedonas G, Pereyra F, Walker B, Kaul R, et al. Increased HIV-specific CD8+ T-cell cytotoxic potential in HIV elite controllers is associated with T-bet expression. *Blood.* 2011 in press.
56. Glimcher LH, Townsend MJ, Sullivan BM, Lord GM. Recent developments in the transcriptional regulation of cytolytic effector cells. *Nat Rev Immunol.* 2004; 4:900–911. [PubMed: 15516969]
57. Fellay J, Shianna K, Cirulli E, McElrath J, Casimiro D, Geraghty D, Frahm N, Goldstein D. A genome-wide association study of host genetic determinants of T cell responses to the MRKAd5 HIV-1 gag/pol/nef vaccine in the Step trial. *AIDS Vaccine.* 2009; Paris, France. 2009.
58. Migueles SA, Rood JE, Berkley AM, Guo T, Mendoza D, Patamawenu AA, Hallahan CW, Cogliano NA, Frahm N, Duerr A, et al. Trivalent adenovirus type 5 HIV recombinant vaccine primes for modest cytotoxic capacity that is greatest in humans with protective HLA class I alleles. *PLoS Pathog.* 2010 In Press. This is the first study to examine CD8+ T cell cytotoxic capacity in vaccine recipients with highly quantitative assays. Although vaccinee responses were similar to those of progressors and lower than those of LTNP, they were significantly higher in individuals carrying protective HLA class I alleles, suggesting efficient T cell priming may be the mechanism by which these alleles mediate their protective effect.

Key Points

1. Virus-specific CD8⁺ T cells are responsible for mediating control over lentiviral replication.
2. More recent measurements of qualitative features of HIV-specific CD8⁺ T cells, including increased perforin expression following stimulation and preserved proliferative capacity, are better determinants of immune-mediated control than traditional quantitative measurements of cytokine-secreting cells.
3. Granule exocytosis-mediated elimination of HIV-infected CD4⁺ T cells by expanded HIV-specific CD8⁺ T cells is the function that most clearly distinguishes the cells of LTNP from those of progressors.
4. Preliminary data suggest observations made in chronically HIV-infected patients may bear important similarities to HIV vaccine recipients and, therefore, contribute to our understanding of vaccine-induced immunologic control.