Avoiding the kiss of death: how HIV and other chronic viruses survive
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Virus-specific CD8 T cells during chronic infection often exceed in numbers virus-replicating infected cells. Why then do antiviral CD8 T cells not do a better job of controlling infection? Although viral strategies for immune evasion are well known, this review will focus on changes in the CD8 T cell that interfere with cytolysis. Most antiviral CD8 T cells in chronic infection do not express perforin, a molecule that is required for cytolysis. IL-2 and other costimulatory signals can restore cytotoxicity that has been impaired, suggesting a role for CD4 T cell anergy. The chance to eradicate an infection by T cell mediated lysis is undermined after an infection becomes established, in part because the effector immune response is impaired in the setting of chronic antigen.

Introduction
Antiviral CD8 T cells able to lyse virus-infected cells are important in controlling viral replication during primary infection. This has been most clearly demonstrated in perforin knockout mice and by the increase in viral burden in macaques depleted of CD8 T cells before SIV infection [1–3]. However, the protective role of virus-specific CD8 T cells during chronic infection is less clear. Recent class-I-MHC–peptide tetramer studies suggest that the numbers of virus-specific CD8 T cells against HIV, Epstein–Barr virus (EBV) or cytomegalovirus (CMV) during chronic human infection generally exceed the numbers of infected cells actively replicating virus [4,5]. Since CD8 T cells are ‘serial killers’ that are able to destroy multiple targets, the question arises as to why they do not do a better job of controlling infection. Each of these viruses has developed strategies to avoid T cell recognition by interfering with antigen processing and presentation and by viral sequence mutation (reviewed in [6]). This review will focus on recent studies looking at the other side of the coin — changes in the CD8 T cell that interfere with its cytotoxic function during chronic infection.

In HIV infection (undoubtedly the best-studied human infection), antiviral cytotoxicity, and in some cases cytokine production by CD8 T cells, is impaired, but can be restored by overnight exposure to IL-2 (reviewed in [5]). Because CD8 cell functional defects are reversed with helper cell cytokines and because CD4 T cell numbers and function are deranged in HIV infection, it has been suggested that CD8 T cell functional impairment may be restricted to HIV-specific CD8 T cells or peculiar to HIV infection [7,8*]. On the basis of recent studies of CD8 T cells specific for other chronic human viruses and in mice, we will argue that impaired antiviral cytotoxicity during chronic infection is not specific to HIV or other situations of CD4 T cell depletion, but is likely to represent regulation of the immune response in the face of chronic antigenic exposure.

Perforin is the rate-limiting protein for CD8 antiviral cytotoxicity
Antigen-specific CD8 T cells contain viral replication by several mechanisms. The most powerful and direct mechanism is cytolysis of infected cells expressing latent or lytic viral antigens. CD8 T cells also control infection by elaborating soluble molecules that suppress viral replication or cytokines — such as IFNγ — that enhance immune responsiveness.

In this review we focus on CD8 T cell mediated cytotoxicity. Granule exocytosis leading to perforin-facilitated induction of apoptotic cell death by the cytotoxic T lymphocyte (CTL) granule proteases (granzymes) is the predominant mechanism of immune-mediated elimination of virus-infected cells [1,9]. Because — provided perforin is available — any of several granzymes can induce cell death independently, perforin is the rate-limiting protein for granule-mediated cytotoxicity. Mice genetically deficient in perforin, or humans with the familial hemophagocytic lymphohistiocytosis syndrome with mutations in the perforin gene, are highly susceptible to a number of viruses, but mice deficient in granzymes A and/or B are only mildly immunodeficient [10–12]. Perforin may also play a role in the activation-induced cell death (AICD) of effector CTLs [13–15]. Granzyme A is expressed more widely than perforin by human CD8 T cells. In normal donors (n=5), 27% ± 8% (mean ± standard error) of circulating CD8 T cells stain for granzyme A, whereas 6% ± 2% are perforin*; in HIV-infected donors (n=11), two thirds of CD8 T cells are granzyme-A+, whereas only one third are perforin* [16*]. This suggests that perforin is the key regulated cytolytic molecule.

Steps in CD8 T cell differentiation into effector CTLs
Until recently, CD8 T cells were thought to belong to three sequential differentiation states: naïve cells that have never seen antigen; effector CTLs with immediate cytolytic function; and memory cells, which are functionally quiescent, but can rapidly be mobilized to become effector cells (Figure 1).
CD8 T cell development is altered in the setting of persistent antigen (Ag). (a) During an acute infection that is cleared, naïve cells exposed to antigen undergo clonal expansion and can then differentiate into effector cells. Stimulation of perforin expression, which is needed for cytotoxic function, requires IL-2, which previously unstimulated cells produce. Most effector cells die of AICD. Memory cells were previously thought to arise only from effector cells that escape apoptosis (and some may), but memory cells can also develop directly from partially differentiated CD8 T cells. In a mouse model, this step occurs if IL-2 concentrations are low or zero and is stimulated by other cytokines, such as IL-15 or IL-7 ([24•]; N Manjunath, unpublished data). An analogous model with similar cytokine dependence is conjectured for human cells. (b) In the setting of persistent antigen, less IL-2 is available because of CD4 T cell anergy. Upon repeated antigenic stimulation, most CD8 T cells become anergized and are not capable of cytotoxicity. Anergy can be broken (at least in vitro) by supplying high concentrations of IL-2 or other costimulatory signals.
Naïve CD8 T cells take 4–5 days to differentiate after their first encounter with antigen to express the cytolytic molecules, granzymes and perforin. The naïve cells modify their cell surface phenotype to downmodulate molecules — such as CCR7 and CD62L — that target them to lymphoid tissues. They also express other molecules — such as β1 and β2 integrins — which allow them to traffic to tissues and adhere more avidly with targets.

No specific cell surface marker uniquely identifies effector CTLs, but CD27 downmodulation and CD56 and 2B4 expression are the cell surface changes that correlate best with perforin expression on CD8 T cells [17–19]. The functional importance of some of the changes in cell surface phenotype is not completely understood. For example, downmodulation of the TNF receptor family member CD27 accompanies CTL differentiation, but it is uncertain whether it is coincidental, whether it is required for cytolysis or whether engagement with its counter-receptor CD70 is required to induce CTL differentiation [20,21]. CD27 engagement seems to be required to generate CD8 memory cells, since mice genetically deficient in CD27 or CD70 functionally lack CD8 memory T cells [20,21]. CD27 engagement appears to be required to generate CD8 memory cells, since mice genetically deficient in CD27 or CD70 functionally lack CD8 memory T cells [20,21].

Effector cells are generally considered to be terminally differentiated cells without proliferative capacity, which are prone to apoptosis and disappear from the body when an infection resolves. Until recently it was thought that memory cells arise from the small numbers of effector cells that survive apoptosis [22,23]. A recent study, however, shows that in mice CD8 memory cells can develop directly from naïve cells, bypassing effector cell differentiation depending on the cytokine milieu [24*]; in the presence of high concentrations of IL-2, effector differentiation occurs; in the presence of IL-15 and absence of IL-2, memory cells develop. In light of the direct pathway for memory cell generation, the idea — based on adoptive transfer experiments — that memory cells develop from effector cells may need to be re-examined. Because many fewer memory than effector cells are generated during an infection, a small contamination of memory cells or memory precursor cells without effector function in adoptive transfer experiments could lead to erroneous conclusions.

Recent studies show that antigen-experienced CD8 T cells cannot be neatly classified as distinct populations of effector and memory cells. When human CD8 T cells are costained for CD45RA or CD62L and the lymph node trafficking molecule and chemokine receptor CCR7, naïve CD8 T cells are CD45RA+CD62L+CCR7+, long-term memory cells are CD45RA−CD62L−CCR7+ and effector CTLs are mostly CD45RA−CD62L−CCR7− [25*]. However, Sallusto et al. [25*] identified a distinct additional population of CD45RA−CCR7− CD8 T cells, confusingly termed ‘effector memory’ cells, in the blood of normal individuals. This population of cells has properties intermediate between memory and effector cells and is greatly expanded in HIV-infected donors, where it constitutes the majority of circulating CD8 T cells [16*]. Several recent studies show that perforin expression and cytotoxic capability are not limited to CD45RA+ cells, so that the ‘effector memory’ cells also include effector cells ([26]; D Zhang et al., unpublished data). The phenotypic properties of ‘effector’ and ‘effector memory’ cells are quite diverse in normal and HIV-infected individuals ([26,27]; D Zhang et al., unpublished data). The heterogeneity may indicate subpopulations with different levels of immediate functional competence or readiness to produce cytokines or to become cytolytic, depending on the activating conditions. Many of these cells may be anergic.

The CD8 T cell differentiation program can be altered by the stimulating conditions. Although the differentiation program of naïve CD8 T cells has been well described for conditions of maximal stimulation, experiments in mice suggest that the quality of activation (strength of TCR engagement, and costimulatory or inhibitory interactions) can lead to different functional outcomes [28–31]. In particular, a strong Ca2+ influx is required to induce cytotoxic capability in naïve cells. This makes sense since all CD8 T cells are positively selected to recognize self antigens and immunopathology could ensue if weak stimuli led to induction of cytotoxicity. How long the key cytolytic molecules are upregulated after activation is uncertain.

Not much is known about the activation of cytotoxicity in different subpopulations of antigen-experienced CD8 T cells compared with naïve cells. Many antigen-specific CD8 T cells in the setting of chronic antigen — whether virus, tumor or autoimmune stimulus — have downmodulated key signaling molecules, including CD3ζ and CD28 [32–36]. These changes are likely to increase the threshold for activation and alter the cell’s response to activation. For example, human and mouse CD8 T cells with downmodulated CD3ζ and CD28 do not produce IL-2 or express the α chain of the high affinity IL-2 receptor upon activation, making them more dependent on local antigen-specific CD4 helper cells [24*,36–38,39*]. Moreover, other signaling differences have been described after activation [33]. CD8 T cells are more likely to express inhibitory NK-like receptors, which may interfere with T cell triggering of cytolytic function [40–42]. Other changes associated with terminally differentiated effector CTLs, such as re-expression of CD45RA, may reduce the potency of activation of the Ras pathway during antigen exposure [43].

**Regulation of perforin expression**

Human long-term memory cells do not express perforin [25*]. Several mouse studies have suggested that memory CD8 T cells express some perforin; however, the levels of perforin expression and the degree of cytotoxicity are reduced compared with those of effector CTLs [23,44,45]. The expression of perforin by memory cells in some mouse studies may, however, be an unnatural consequence of homeostasis-driven proliferation following adoptive transfer into lymphopenic RAG knockout mice [46].
other mouse studies where this is not the case, it is clear that memory cells can develop into effector CTLs within 1 day of restimulation, a lag time much shorter than the 4-5 days required for naïve cell differentiation [47,48]. Although human memory CD8 T cells produce IFN-γ rapidly after activation [49], their immediate cytotoxic function has not been studied.

The regulation of perforin protein expression, which we hypothesize to be the controlling factor for cytotoxic function, is not completely understood. Perforin expression is largely, but possibly not completely, regulated at the level of transcription. The promoter determines cell-type-specific expression, but is unexpectedly largely devoid of activation-induced regulatory elements, such as occur in cytokine gene promoters [50]. When the 5’ 5.1 kb promoter region of the perforin gene is used to drive expression of a reporter gene in transgenic mice, the reporter gene is expressed in NK cells and all T cells after the double-negative stage, suggesting that unidentified silencers and repressor factors provide the exquisite specificity of perforin expression only in cytotoxic cells [51]. Candidate regulatory sequences for inhibiting perforin expression, which suggest a role for an Ets family transcription factor in repression, have been identified in two IL-2 dependent upstream enhancers, but the relevant repressor(s) remain unknown [51–53]. The Ets family member Elf-1, which controls CD3ζ expression [54] and is downmodulated in effector cells [24*], is an interesting candidate. Identification of factors that control perforin expression will facilitate understanding the regulation of CTL function in chronic infection.

Signaling through the IL-2 receptor or similar stimuli that activate sustained Ca²⁺ fluxes and Stat5 are required for perforin expression [53,55,56]. Because naïve CD8 T cells express IL-2 and the high affinity IL-2 receptor upon activation, the initial activation of naïve CD8 T cells to proliferate and differentiate into effector CTLs does not require CD4 T cell help, as has been elegantly demonstrated in murine models [57–60].

However, because of changes in key signaling receptors and pathways, previously activated CD8 T cells quickly lose the ability to produce IL-2 [36–38,39*,61]. Moreover, at least in humans, the costimulatory molecules CD28 and CD27 are downmodulated, and activation does not induce the high affinity IL-2 receptor α chain [36,37]. Therefore antigen-experienced CD8 T cells are exquisitely dependent on CD4 T cell help for induction of perforin expression and sustained cytotoxic function. As a consequence, during persistent infection of mice deficient in either CD4 T cells or MHC class II expression, CD8 T cells endure, but without effector CTL function and are unable to control infection as effectively as mice with intact CD4 T cells [57–60,62]. CD4 T cells are also not required to maintain antigen-specific CD8 T cells in humans, since CMV- or HIV-specific CD8 T cells persist at high frequency but without function even in some patients with CD4 counts near zero [63].

**CD8 T cell anergy in mouse models of persistent infection**

In the setting of persistent antigen, CD4 T cells become anergized (or partially anergized). In particular the ability to proliferate in response to antigen is lost. Proliferative capacity is tightly linked to IL-2 production and anergized cells no longer produce IL-2. Therefore, during chronic infection, anergized antigen-specific CD4 T cells are unlikely to provide the critical IL-2 signal required to induce perforin expression on previously activated CD8 T cells.

Recent studies in murine models of chronic infection also demonstrate that CD8 T cells can rapidly lose effector CTL function, independently of CD4 T cell depletion. In one study transgenic CD8 T cells specific for a lymphocytic choriomeningitis virus (LCMV) peptide epitope were transferred into wild-type mice or mice constitutively expressing the epitopic peptide, to mimic persistent infection [60]. Although the transferred transgenic cells proliferated and were activated in the mice expressing the antigen, they rapidly became tolerized and lost cytotoxic capability. However, if these same mice were challenged a few days after transfer with LCMV or another infection or inflammatory stimulus, tolerance was broken (even in CD4-depleted mice) and the CD8 T cells became cytotoxic and induced a graft-versus-host (GVH)-like disease. However, in the chronic phase (after 30 days) although the transferred cells were present in high numbers and showed signs of activation, they lacked cytotoxic function and were unable to control an LCMV challenge. In contrast, the LCMV-transgene-bearing T cells in wild-type mice were not anergic and behaved like memory cells, which conferred protection.

Another study compared the function of adoptively transferred LCMV-specific CD4 and CD8 T cells in mice persistently infected with another strain of LCMV [64]. Whereas the CD4 T cells produce IL-2 and proliferate in response to antigen for at least 1 month after transfer, LCMV-specific CD8 T cells were highly cytotoxic 9 days after transfer, but had largely lost cytotoxic capability 1 week later. In support of these results, persistently infected mice transferred with LCMV-specific CD4 T cells were protected from heterologous challenge for 40 days after transfer, but mice transfected with LCMV-specific CD8 T cells were only protected if challenged by day 9, but not 1-2 months later. Therefore in this model, CD8 T cell anergy develops more rapidly than CD4 T cell anergy. A more recent study also found similar kinetics of loss of IFN-γ production by CD8 T cells when a normally cleared LCMV infection becomes a persistent infection in perforin knockout mice deficient in cytolyis [15].

The γ-herpesvirus also establishes chronic infection, which provides an additional valuable model to explore the
effects of persistent infection on CD8 T cell functional competence [59]. CD4 depletion clearly exacerbates the functional defects in persistently infected mice in this model [65], as it does in LCMV infection [63]. However, which effects on CD8 function are secondary to lack of CD4 help and which are secondary to the higher levels of viral infection in CD4-depleted mice have not yet been clarified in this model.

**CD8 T cell anergy in HIV and SIV infection**

Evidence for CD8 T cell anergy in the setting of human HIV infection was described concurrently with the first mouse models [35]. In many HIV-infected donors, HIV-specific cytotoxic function is barely detected in freshly isolated circulating lymphocytes, but rapidly develops after overnight exposure to high concentrations of IL-2 [8•,35,66,67]. Other costimulatory signals — such as IL-12 or CD40L trimers — also break CD8 T cell anergy in vitro [68]. Moreover, the vast majority of tetramer-labeled HIV-specific CD8 T cells do not express perforin, and the lymphoid tissues of HIV-infected donors are virtually devoid of perforin-staining cells [8•,69]. Although studies in humans are never as clear-cut as in the mouse because of the hard-to-control heterogeneity of infected people and inherent limitations on experimental manipulation, understanding the functional properties of CD8 T cells in the setting of chronic human infection (which may not be precisely the same as in the mouse) is essential to develop immune-based interventions for increasingly devastating illnesses caused by persistent human viruses, including HIV, CMV, EBV, hepatitis B virus and hepatitis C virus (HCV). Moreover, the lessons from chronic infection are also likely to be highly relevant for manipulating CD8 T cell responses in other settings of persistent antigen, such as for treating tumors or preventing autoimmunity.

Cytotoxicity is not the only CD8 function that is impaired. Only a fraction of tetramer-labeled HIV-specific CD8 T cells produce IFNγ upon restimulation, although this immune function is less compromised than specific cytotoxicity in some patients and the literature on this is not consistent [8•,67,70,71]. Interestingly some studies that show no defect in cytokine production use costimulatory antibodies in addition to antigen to stimulate cytokine production, which may break anergy, and others may be looking at patients with less-advanced disease [8•,71]. These results taken together suggest that CD8 T cells in chronic infection may have different degrees of anergy, with compromise of cytotoxic function occurring before compromise of IFNγ production.

Recent studies in SIV-infected macaques also show CD8 T cell dysfunction with persistent infection. In one study it was shown that, although virtually all SIV-tetramer+ CD8 T cells produced IFNγ after vaccination or early after infection, the proportion of specific cells producing IFNγ fell substantially within 6 months [72•]. In another study, CD8 T cells from macaques who failed to control SIV infection, as evidenced by detectable plasma viremia and falling CD4 T cell counts, had impaired specific cytotoxicity and secretion of IFNγ and TNFα, particularly at mucosal sites of infection, compared with macaques with controlled viremia [73].

**Human CD8 T cell anergy is not unique to HIV infection**

Because SIV or HIV infection specifically targets CD4 T cells, the question remains about whether impaired CD8 T cell cytotoxicity in humans is specific to HIV-specific CD8 T cells or to HIV infection. Only a few studies have addressed this question and their conclusions differ.

In one study perforin staining and cytotoxic function by HIV- or CMV-specific CD8 T cells were different. In 11 HIV-infected samples, an average of about 40% of CMV-tetramer+ cells stained for perforin, whereas only somewhat over 10% of HIV-tetramer+ cells in the same donors were perforin+ [8•]. However, in our study of 35 HIV-infected and 10 normal donors, there was no significant difference in perforin expression in HIV-, EBV- or CMV-specific CD8 T cells whether from HIV-infected or normal donors (D Zhang et al., unpublished data); in each case, an average of 16%–22% of tetramer+ CD8 T cells stained for perforin. In both studies the phenotype and presumably functional capabilities of human antigen-experienced CD8 T cells studied by tetramer labeling were quite heterogeneous. In particular, there was considerable heterogeneity in the proportion of perforin+ specific cells (reaching up to 75% of tetramer+ cells in rare samples). This suggests that differences in viral load and antigen-specific CD4 T cell function, as well as in other immune and host genetic variables that are perhaps unknown, in different hosts will have a large impact on whether effective specific cytotoxicity continues during persistent viral infection.

Not surprisingly, both studies (8• and D Zhang et al., unpublished data) found that perforin expression was required for cytotoxic function. Although perforin expression by T cells specific for these three chronic viruses was indistinguishable in our study (D Zhang et al., unpublished data), all studies agree that HIV-specific cells are less likely to have other phenotypic properties of effector CTLs, such as CD27 downmodulation and CD45RA expression, than EBV- or CMV-specific cells in HIV-infected donors (8•,27; D Zhang et al., unpublished data).

A recent study of five donors persistently infected with HCV also showed impaired IFNγ and TNFα production by HCV-specific CD8 T cells, which was more widespread than in EBV- or CMV-specific CD8 T cells [74]. However, even for those viruses, only a fraction of tetramer+ cells secrete cytokines after antigenic stimulation; in contrast, in mouse models of cleared infections every memory cell is capable of cytokine production when stimulated [62].
In another paper that studied patients with chronic EBV infection, the phenotypic properties of CD8 T cells responding to EBV latent antigens were those of long-term memory cells, whereas T cells specific for lytic antigens were very heterogeneous in expression of markers associated with CTL effector state [26]. This suggests that the EBV latent antigens may be weakly presented in chronic EBV infection, allowing CD8 T cells specific for latent antigens to develop into true memory cells, providing a functional reserve at times of viral recrudescence. EBV-specific cytotoxic activity and cytokine production were heterogeneous by these mixtures of long-term memory, effector and anergic CD8 T cells, and did not correlate with the markers that have been attributed to effector CTLs.

With increasing EBV viral load in immunosuppressed HIV-infected donors, the ability of EBV-specific CD8 T cells to produce IFN-γ is compromised compared with normal donors [75]. Moreover, their functional capacity is even more limited in more-advanced patients with AIDS or lymphoma.

**Figures 2**

Persistent antigen or CD4 depletion leads to CD8 T cell anergy. Viral load, CD8 T cell numbers and CD4 and CD8 T cell function are modeled for different viral conditions. IL-2 is produced by both CD4 and CD8 T cells immediately after infection, but later on is largely produced by CD4 T cells; cytotoxicity is largely by CD8 T cells. (a) In a cleared infection, virus is cleared coincident with the expansion of functional antigen-specific CD4 and CD8 T cells. After the virus is cleared, specific memory cells persist indefinitely and are available for an accelerated response to reinfection. (b) If CD4 T cells are absent, the virus is more likely to persist, but CD8 T cells become unable to lyse infected cells. (c) In a well-controlled persistent infection with low levels of viral replication—such as EBV infection in immunocompetent hosts—antigen-specific CD4 and CD8 T cells are able to function to control low levels of infection or small spurts in viral activity as they occur. (d) In viruses that are less well controlled, CD4 and CD8 function is more severely compromised and may eventually lead to lack of immune control of the infection. This situation, because of T cell anergy, resembles that of a normally cleared infection in the setting of CD4 T cell depletion (b). (e) Eventual lack of immune control is more likely to develop if the virus (such as HIV or SIV) infects or disables CD4 T cells; in that setting, viral burden also is increased. (f) Controlling viral replication with drugs, particularly during the first weeks or months after infection, reduces viral burden and can block the development of T cell anergy, leading to a well-controlled infection, such as (c). Later interventions with therapeutic vaccination or other immunomodulatory approaches may be able to break T cell anergy and restore immune control. Because of viral and/or host variability, a small minority of patients infected with viruses such as in (e)—termed long-term non-progressors—have this picture of viral control without antiviral or immune therapy.

**How can CD8 anergy be prevented or reversed in chronic infection?**

These results taken together suggest that, during chronic infection, loss of cytotoxicity is not universal but may be prevented under certain fortuitous circumstances that remain to be defined (Figure 2). CD4 depletion is not required for human CD8 T cell anergy, because it occurs in infections with viruses such as HCV that do not deplete CD4 T cells. However, CD4 depletion will certainly exacerbate the problem of CD8 dysfunction.

Likely relevant factors for continued CD8 T cell function during persistent infection are the presence of...
non-energized antigen-specific CD4 T cells and low antigenic burden (such as in the setting of undetectable plasma viremia and low frequency of cells actively replicating virus). These two factors are highly interdependent variables, since functional CD4 T cells improve the immune response and lead to lower viral load, and lower viral load decreases the likelihood of CD4 T cell anergy.

Other factors that may contribute to whether CD8 T cell anergy develops in the setting of persistent infection are the expansion of various classes of immunoregulatory cells — including CD25+ CD4 T cells and NKT cells — and the elaboration of immunosuppressive cytokines, such as TGFβ and IL-13, by these cells and by antiviral CD8 T cells themselves [76–78,79•,80].

Conclusions

Murine and human studies suggest that CD8 T cell anergy is not peculiar to retroviruses that specifically target CD4 T cells or to situations in which CD4 T cells are deleted. CD4 anergy and high levels of antigenemia also lead to impaired CD8 T cell cytotoxicity. Moreover, each virus has evolved unique ways to interfere with T cell recognition and elimination of infected cells, which have a substantial impact on the persistence of functional CD8 T cells during the chronic phase of infection. In particular, in HIV infection, many HIV gene products, including env, nef, tat and vpr, have profound effects on T cell activation, which may influence the development of CD8 T cell anergy (these studies are too numerous to reference here).

Continued CD8 T cell functional competence, and in particular antiviral cytotoxicity, is likely to be critical for effective immunosurveillance in the setting of persistent infection. During chronic infections CD8 T cell anergy is widespread. CD8 dysfunction, present at different levels with cytokine function more extensively compromised than cytokine production, is exacerbated by CD4 T cell anergy and depletion, and by high levels of persistent antigen and viral replication. Viral factors that interact with antigen processing and presentation, and T cell activation, as well as viral sequence mutation to evade T cell recognition, also affect the effectiveness of CD8 T cells. CD8 anergy can be broken or avoided by removal of antigen or by supplying costimulatory signals that substitute for CD4 T cell help. This suggests that therapeutic efforts to establish effective immune surveillance for poorly controlled viral infections such as HIV should focus on controlling viral replication to reduce levels of antigen and on inducing or replacing CD4 costimulatory signals, which might be provided by therapeutic immunization, replacement therapy with cytokines, or costimulatory ligands or antibodies.

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