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CD8 T cell persistence in treated HIV infection

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Abstract

Purpose of review—Many treated HIV infected persons maintain persistently high circulating CD8 T cell numbers, even after many years of therapy. Recent reports suggest that persistent CD8 T cell expansion is associated with higher risk of morbid non-AIDS events. Thus, assessing the mechanisms of CD8 T cell expansion and persistence may give insights into a feature of HIV disease that is clinically important.

Recent findings—Acute HIV infection is associated with activation and expansion of the CD8 T cell compartment. Expanded CD8 T cells persist throughout disease course and, in contrast to the plasticity that typically characterizes immune responses to most other pathogens, circulating CD8 T cell numbers do not normalize in many patients despite pharmacological suppression of HIV replication. We suspect that residual inflammation in treated HIV infection contributes to antigen-independent CD8 T cell expansion and persistence as most of these cells are not HIV-reactive.

Summary—Circulating CD8 T cell numbers remain abnormally elevated in many treated HIV-infected patients and this elevation is associated with adverse clinical events. Future studies will need to assess the mechanisms of CD8 T cell expansion and to define the role of CD8 lymphocytosis in the clinical course of treated HIV disease.

Keywords

Bystander T cell activation; CD8 lymphocytosis; HIV-1; morbidity; mortality

Introduction

The dynamics of the CD8 T cell response largely shape the overall course of viral infections. Upon antigen encounter, virus-specific CD8 T cells become activated and undergo a program of clonal expansion. This expansion phase is accompanied by cellular changes that are controlled at the transcriptional level. The induction of peripheral tissue homing receptors, downregulation of homeostatic cytokine receptors, and upregulation of effector molecules such as granzyme B and perforin are all components of the antiviral CD8 T cell response (1–3). After the expansion phase, a large proportion of effector cells will die by

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apoptosis whereas some of the surviving CD8 T cells will go on to form memory (4). Virus-specific memory CD8 T cells regain the capacity to proliferate in response to homeostatic cytokines such as IL-7 and IL-15 and can persist in the absence of antigen, forming a long-lasting protective mechanism upon antigen re-exposure (5, 6).

The loss of virologic control in SIV-infected rhesus macaques treated with CD8-depleting antibodies highlights the critical importance of CD8 T cells in viral control (7). Acute HIV infection follows similar dynamics of effector CD8 T cell expansion as is seen in other viral infections (8–10). Unlike other viral infections however, the expansion of the CD8 T cell compartment is not limited only to HIV-reactive cells, and CD8 T cell numbers typically remain elevated throughout the disease course (11, 12). Upon control of viremia with antiretroviral therapy (ART), the expanded CD8 T cell compartment tends to contract a bit yet remains elevated in many persons despite virological suppression, even after many years of therapy (13). In this review, we will discuss the biological and clinical significance of CD8 T cell persistence in HIV infection, touching upon the dynamics of their initial expansion in HIV infection, their phenotypic and functional characteristics, and the potential mechanisms that mediate CD8 T cell persistence in ART-treated HIV infection.

Evidence of bystander CD8 T cell expansion in acute HIV infection

The immune response in acute HIV infection may have a considerable effect on long-term disease course. Marked activation of the CD8 T cell pool is well characterized in primary HIV infection and is partially attributed to the activation of HIV-specific CD8 T cells. Yet even under conditions of high viral replication, HIV-specific CD8 T cells only represent <10% of the total CD8 T cell pool and cannot account for all CD8 T cells that are seen to be activated in acute and chronic infection (14, 15). CD8 T cells reactive to microbes other than HIV are also induced to expand during this period. Some of this may be due the reactivation of latent pathogens such as Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) (16). Yet, CD8 T cells reactive to non-persistent pathogens such as influenza and adenovirus are also induced to expand, implying that CD8 T cell expansion occurs through antigen-independent mechanisms as well (17). In contrast, in the CD4 T cell compartment, expansion of cells reactive to persistent pathogens such as herpes viruses is demonstrable but CD4 T cell responses to non-persistent antigens are unaffected (18). It isn't clear why bystander expansion occurs in the CD8 T cell compartment but not the CD4 T cell compartment in primary and early HIV infection although the susceptibility of activated CD4 T cells to lytic HIV infection may blunt bystander activation of CD4 T cells in this setting.

Does bystander CD8 T cell activation occur in other viral infections? In mice, the CD8 T cell response to LCMV infection is largely antigen-driven, where tetramer staining of virus-specific cells reveal that as many as 56% of activated CD8 T cells stain positive for a single LCMV epitope (19). While less is known about the early CD8 T cell response to viral infections other than HIV in humans, subjects vaccinated with smallpox and yellow fever vaccines display minimal activation of CD8 T cells specific for other pathogens such as CMV, EBV, or influenza (20). Whether the lack of bystander CD8 T cell activation in this setting is related to the self-limited replication of attenuated vaccine viruses versus the

persistent replication of HIV is unknown. Nonetheless, it is apparent that CD8 T cell expansion during acute HIV infection is not limited to CD8 T cells that are HIV-specific. Furthermore, the broad CD8 T cell expansion that is demonstrable in early infection persists throughout disease course (21).

Circulating CD8 T cell numbers remain elevated throughout the course of HIV infection

In healthy individuals, the majority of circulating CD8 T cells comprise naïve and central memory CD8 T cells that co-express CD27 and CD28. During chronic HIV infection, the CD8 T cell compartment is enriched for more mature effector and effector memory CD8 T cells that have lost CD27 and CD28 presumably as a result of antigenic exposure (22) (12). The expanded CD8 T cell compartment in chronically HIV infected subjects exhibits characteristics of T cell exhaustion and immunosenescence, phenotypes associated with disease progression (23, 24).

Exhaustion is characterized by a progressive loss of T cell function and develops under conditions of high antigen load during persistent viral infections such as HIV, HCV, and EBV (25–27). In HIV infection, exhaustion of CD8 T cells is associated with impairment of antiviral effector functions. These include limited proliferative capacity in response to antigen, reduced cytokine production, and high susceptibility to apoptosis *in vivo* (28–31). Functional impairments associated with CD8 T cell exhaustion are the result of signaling by inhibitory receptors expressed on the surface of CD8 T cells, such as PD-1, CD160, or Tim-3 (32). Importantly, some of the functional defects of T cell exhaustion can be reversed through blockade of these inhibitory receptors (29, 33).

Persistent viral infections such as HIV are also characterized by increased CD8 T cell immunosenescence. Similar to exhaustion, T cell senescence can arise from sustained antigen exposure. Here, the many rounds of proliferation in the setting of chronic viral infection (24, 34) result in shortening of the telomeric ends of cellular DNAs. These senescent T cells are defined by expression of CD57 and loss of CD28. Like “exhausted” CD8 T cells, senescent CD8 T cells do not proliferate in response to antigen (24). Growth arrest in this population is related to telomere erosion; CD57-expressing CD8 T cells have significantly shorter telomeres than other less differentiated CD8 T cell subpopulations (24, 35).

While some features of T cell exhaustion and T cell senescence are overlapping, a number of findings indicate that these processes can exist independently of one another (36). For example, unlike exhausted CD8 T cells which are characterized by a progressive lack of functionality, CD57+ senescent CD8 T cells are highly cytotoxic, and generally exhibit a much higher degree of polyfunctionality than exhausted CD8 T cells (37–40). Nevertheless, exhaustion markers can indeed be expressed on late-differentiated senescent CD8 T cells, and microarray data indicates that senescent CD8 T cells can show gene signatures of exhaustion (41, 42). Thus, it is likely that a senescent cell can become exhausted, yet at the same time, exhaustion and senescence can also be induced independently of one another. A

description of similarities and differences between these two processes is illustrated in Figure 1.

Persistently high circulating CD8 T cell numbers in treated HIV-infected subjects are associated with adverse clinical events

Despite a dramatic decay in HIV-specific CD8 T cell numbers upon ART administration (43) (44) absolute CD8 T cell counts diminish only minimally during the first year of therapy and then remain relatively stably expanded for years thereafter (21, 45). As a result, many ART-treated patients maintain persistently high circulating CD8 T cell numbers (21, 45). As CD4 T cell numbers are often lower than among controls, these patients often display inverted CD4/CD8 ratios. A recent study examined the characteristics of CD8 T cells in patients with inverted CD4/CD8 ratios despite sustaining CD4 T cell counts above 500 cells/ul on ART. In this study, inverted CD4/CD8 ratios were associated with higher absolute numbers of circulating transitional memory, effector memory and terminal effector CD8 T cells (45). Patients with lower CD4/CD8 ratios also had higher absolute numbers of activated CD38 and HLA-DR co-expressing CD8 T cells, exhausted PD-1-expressing CD8 T cells, and senescent CD28-CD57+ CD8 T cells than did treated HIV-infected patients with CD4/CD8 ratios over 1.0 (45).

Despite effective ART, HIV-infected patients are at a higher risk for non-AIDS morbidities and mortalities than the general population (46, 47). A number of studies have found that soluble mediators of inflammation and coagulation such as IL-6, D-dimer, and soluble CD14 are independent predictors of non-AIDS morbidities and mortalities (48). In a recent study examining the relationship between the CD4/CD8 ratio and serious non-AIDS events, subjects who experienced a morbid non-AIDS event during the time of study had lower CD4/CD8 ratios than subjects who did not (49). This was the case for all types of non-AIDS events such as stroke, non-AIDS malignancies, and ischemic heart disease (49). Noteworthy, these associations were independent of CD4 nadir or proximal CD4 T cell counts.

To date, mechanistic evidence that links persistently high circulating CD8 T cells to the occurrence of non-AIDS morbid events is lacking. We have recently found that the expanded CD8 T cell compartment in treated HIV-infected patients is enriched for cells co-expressing the fractalkine receptor, CX3CR1, and the Protease-activated receptor-1 (PAR-1). CX3CR1 is a G-protein coupled receptor that binds CX3CL1 expressed on activated endothelial cells whereas PAR-1, another G-protein coupled receptor, can become activated through cleavage of the N-terminal end of the receptor by thrombin, a zymogen activated during coagulation (50, 51). Thus, CD8 T cell persistence in treated HIV-infected subjects may result in increased frequencies of circulating CD8 T cells that localize to endothelium and that may be activated during coagulation that is accelerated in HIV infection (52). More studies are needed to ascertain whether the persistent CD8 T cell expansion in treated HIV infection contributes directly to the occurrence of non-AIDS morbidities and mortalities or whether it is a consequence of other events that themselves drive these clinical outcomes.

What are the determinants of CD8 T cell persistence in treated HIV infection?

The factors that underlie persistent CD8 expansion in treated HIV infection remain largely unidentified. While residual HIV has been found in tissue sites in treated HIV-infected subjects (53), it is not likely that HIV antigens drive persistent CD8 T cell expansions as HIV-specific T cells decrease in frequency with initiation of ART and comprise <1% of circulating CD8 T cells in treated HIV-infected patients (54, 55).

Could the presence of other pathogens such as CMV be responsible for CD8 T cell persistence in treated HIV infection? Frequencies of CD8 T cells specific for the CMV epitope Intermediate-early-1 protein (IE-1) are increased in treated HIV-infected patients (56). Yet, the extent to which CMV-specific CD8 T cells contribute to the overall size of the CD8 T cells pool in treated HIV infection is still unclear, as CMV-specific CD8 T-cells comprise only a fraction of the expanded memory CD8 T cell pool in treated HIV-infected patients. Thus, other factors likely contribute to the persistence of CD8 T cells in this setting.

If not antigen, what may be responsible for CD8 T cell persistence in treated HIV infection? HIV infection, both untreated and treated is characterized by chronic inflammation. Microbial translocation through a persistently damaged gut epithelium is one potential contributor to sustained inflammation in this setting (57–59). Importantly, gut damage sustained during the acute phase of HIV infection is not completely reversible even after ART (60), and levels of microbial products remain increased in the systemic circulation of many ART-treated patients (61) (58).

Microbial elements bind specific pathogen-associated molecular pattern receptors on antigen presenting cells (APCs) to induce pro-inflammatory cytokines; some of these can induce activation and proliferation of CD8 T cells in an antigen-independent manner (17). IFN- α can be induced by DCs primed with microbial products and in mice, IFN- α has been shown to induce memory CD8 T cell proliferation in an antigen-independent fashion (62, 63). Because IFN- α is increased systemically in untreated HIV infection and treated HIV-infected patients display type I interferon gene signatures (64, 65), it is possible that sustained exposure to type I interferon's could contribute to CD8 T cell persistence in treated HIV infection.

IL-15 is another cytokine induced by LPS-primed APCs (17). In mice, the absence of IL-15 led to slow attrition of memory CD8 T cells generated during acute LCMV infection (66), indicating that IL-15 is important in maintaining memory CD8 T cell persistence. Indeed, a number of studies have shown in both humans and mice that IL-15 induces memory CD8 T cell proliferation and increases survival factors such as bcl-2 (17, 67). In primates, IL-15 administration resulted in a preferential expansion of effector memory CD8 T cells, resulting in an inverted CD4/CD8 ratio (68), although this was not sustained after IL-15 administration was stopped.

Our group has shown that IL-15 levels are increased in lymph node histocultures of chronically infected untreated HIV infected patients (69) although it isn't clear whether IL-15 expression remains increased in treated HIV infection. Recently, we and others have reported increased levels of IL-1 β in the lymphoid tissues of untreated and ART-treated HIV infected patients and have found that IL-1 β can promote the expansion of memory CD4 and CD8 T cells in vitro without addition of exogenous antigen (70, 71). It is plausible that sustained expression of inflammatory cytokines such as IFN- α IL-1 β and IL-15 play a role in the profound and persistent memory CD8 T cell expansion that characterizes HIV infection.

The intrinsic properties of CD8 T cells may also contribute to their persistence in treated HIV infected individuals. In conditions other than HIV infection that result in lymphopenia such as sepsis or chemotherapy, homeostatic proliferation stimulates the reconstitution of CD8 T cells much faster than that of CD4 T cells (72, 73). In addition, deuterated glucose labeling in HIV infected subjects revealed that CD8+ T cells are much less susceptible to cell death than are CD4 T cells in vivo (74). It remains to be determined whether those CD8 T cells that are expanded in treated HIV-infected patients persist through continued cell division. We have found that the cycling of circulating CD8 T cells in patients who have suppressed HIV replication with ART is not elevated irrespective of whether they have restored circulating CD4 T cell numbers (75). Thus it is also plausible that these cells, once expanded and matured, persist durably without additional divisions.

Conclusions

Despite effective ART, many patients display residual immune dysregulation and remain at higher risk for non-AIDS defining adverse clinical events. While elevated inflammatory indices have been the most studied laboratory correlates of this increased risk, recent epidemiologic data also link CD8 T cell expansion and lower CD4/CD8 ratios to these morbidities. While the majority of these expanded CD8 T cells are matured effector cells that are capable of inflammatory cytokine release, the cause of these expansions is not known and their mechanistic link to the morbid complications of treated HIV disease are only speculative.

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Key points

- HIV infection is characterized by CD8 T cell activation and expansion, much of which is “bystander”
- Circulating CD8 T cell numbers remain elevated in ART-treated patients
- Inverted CD4/CD8 ratios in ART-treated subjects are associated with non-AIDS related morbidities and mortalities.

Figure 1. Characteristics of T cell exhaustion and T cell immunosenescence that are both overlapping and distinct

A diagram of similarities and differences between CD8 T cell exhaustion and senescence.