Regulation of CD8+ T-cell cytotoxicity in HIV-1 infection

Alireza Saeidi a, Marcus Buggert b, Karlhans F. Che c, Yong Y. Kong a, Vijayakumar Velu d, Marie Larsson e, Esaki M. Shankar a,f

a Centre of Excellence for Research in AIDS (CERiA), Faculty of Medicine, University of Malaya, Lembah Pantai, Kuala Lumpur, Malaysia
b Department of Microbiology, University of Pennsylvania, USA
c Institute for Environmental Medicine, Karolinska Institute, Solna, 17 177 Stockholm, Sweden
d Department of Microbiology and Immunology, Emory University, GA, Atlanta, USA
e Division of Molecular Virology, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden
f Tropical Infectious Diseases Research and Education Centre, Department of Medical Microbiology, University of Malaya, Lembah Pantai, Kuala Lumpur, Malaysia

ABSTRACT

Understanding the mechanisms involved in cellular immune responses against control of human immunodeficiency virus (HIV) infection is key to development of effective immunotherapeutic strategies against viral proliferation. Clear insights into the regulation of cytotoxic CD8+ T cells is crucial to development of effective immunotherapeutic strategies due to their unique ability to eliminate virus-infected cells during the course of infection. Here, we reviewed the roles of transcription factors, co-inhibitory molecules and regulatory cytokines following HIV infection and their potential significance in regulating the cytotoxic potentials of CD8+ T cells.

1. Introduction

Cytotoxic T lymphocytes (CTLs) are critical effector CD8+ T cells important in the clearance of viruses, intracellular bacteria and tumors in the host [1,2]. Notwithstanding effector CD8+ T cells remain the well-recognized CTLs in humans, CD4+ CTLs have also been reported previously [3]. CTLs are believed to destroy target cells through either non-cytotoxic or cytotoxic mechanisms. The cytotoxic machinery operates mainly via two principal routes that include the Fas–Fas ligand (FasL) pathway and granule exocytosis (GE) [4,5]. In the Fas–FasL pathway, FasL is up-regulated on CD8+ T cells following activation by a target cell [6]. The subsequent engagement of FasL with Fas results in the activation of the caspase cascade ultimately leading to apoptosis of the target cell [7,8]. On the other hand, the GE pathway involves the release of cytotoxic granules held within specialized secretory lysosomes by effector cells into the immunological synapse to specifically destroy viral-infected target cells [9,10]. Cytotoxic granules contain many proteins, especially perforin and a group of serine proteases called granzymes, which are located in the proteoglycan matrix [1,2]. Perforin, a calcium-dependent pore-forming protein having a homology to complement components, delivers granzymes into the target cell cytosol [11]. Perforin allows granzymes to access their substrates although there are several views on exactly how the synergy occurs between them [12]. Rapid up-regulation and granule-independent transport of perforin to the immunological synapse has also been defined as a novel mechanism of CTL cytotoxicity [13]. To date, 5 human granzymes (A, B, H, K, M) and 11 mouse granzymes (A–G and K–N) have been identified [14], whereas granzyme A (GrA) and granzyme B (GrB) are the predominant and well-studied of all the granzymes [15,16]. Genetics studies in knockout mice have revealed that perforin and GrB are essential components of granules important in the GE mechanism of target cell death [17–20].

In general, CD8+ CTLs exploit the GE mechanism to destroy target cells by releasing perforin and granzymes, especially GrB [21,22]. These cytolsins are released early after CD8+ T-cell activation into the immunological synapse, and this process of degranulation is MHC class I-restricted and antigen-specific [23]. Although it has been shown that CD4+ T cells lyse target cells via Fas–FasL interactions [24,25], GE-mediated CD4+ T-cell cytotoxicity has also been demonstrated in human infections with human cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein–Barr virus (EBV), influenza virus and HIV [26–31]. Having said that CTLs
have a key function in host immune surveillance, they reportedly play a vital role in host defense against HIV-1, by impeding viral replication through both cytolytic and non-cytolytic pathways [32–34]. The cytolytic pathways include calcium-dependent exocytosis of perforin and granzymes, as well as Fas-mediated programmed cell death [35], whereas the non-cytolytic pathways primarily function by the release of β-chemokines, which block viral entry [36,37]. The majority of HIV-1-specific CD8+ T cells are believed to kill via calcium-dependent exocytosis of perforin and granzyme proteases and there is no clear evidence of a contribution of FasL-mediated killing by HIV-specific CD8+ T cells [38]. Epitope specificity and virus escape are critical to CD8+ T-cell cytotoxicity-mediated control of HIV, and are particularly considerable in vaccine-elicited CD8+ T-cell responses. The current review is a compendium highlighting the critical roles of certain transcription factors, co-inhibitory molecules and regulatory cytokines, and their potential significance in the regulation of the cytotoxic potentials of CD8+ T cells in the context of HIV infection.

2. Quantitative measurement of cytotoxic activity of CTLs

The direct cytotoxic capacity of CTLs has been investigated in vitro using the chromium release assay (CRA) or by a similar fluorescence-based assay to show that HIV-specific CD8+ T cells have direct cytotoxic effects against HIV-infected CD4+ T cells [39–41]. The CRA measures the effects of CTL on target cells without providing any phenotypic or functional characteristics on CTLs by itself [42]. Therefore, the association between the results of CRA assay and the in vivo state has been questioned [43]. Besides, the cytotoxic potentials of CD8+ T-cell can also be investigated directly by flow cytometry. This method determines killing potential based on the content of perforin and granzyme the CD8+ T cells have, whereas it has the advantage to permit measurement of additional parameters, revealing a more complete picture of the cells with killing potentials [42]. The perforin content of antigen-specific CD8+ T cells can also be measured by staining resting cells with MHC class 1 tetramers or by peptide-stimulation. MHC class I tetramer staining may provide sufficient stimulation to induce perforin release, resulting in an under-estimation of perforin content, so sustainability of the cytotoxic response cannot be assessed [42]. To overcome the tetramers method restrictions, Several studies have assessed the serial killing potential via stimulation of CTLs and measuring the perforin content after multiple rounds of proliferation [42,44–46]. It has also been suggested that ELISPOT can lead to ex vivo measurements of perforin and Grb2 secretion, which may permit the distinction between in vivo resting versus activated CD8+ memory T cells in healthy and HIV-infected individuals [47]. This recent study suggests that extending the present standard of IFN-γ measurements to the analysis of perforin and Grb2 release in functional T-cell assays will reveal newer insights into the effector functions of CD8+ T cells.

Bettes and others have also developed an assay that measure CD107a levels on CD8+ T cells as a marker of killing abilities [48]. Besides, this method also describes cytotoxicity as one of the prime mechanisms underlying the revelation of HIV escape mutants [49–51]. Makedonas et al. identified a novel correlate of CD8+ T-cell immunity by measuring newly synthesized perforin following antigen-specific activation [13]. Their new method demonstrated that virus-specific CD8+ T cells rapidly upregulate perforin in response to stimulation. It was also concluded that the rapid appearance of newly synthesized perforin at the immunological synapse is both in association with and independent of cytotoxic granules where it functions to promote cytotoxicity. This finding changed the existing concept that CD8+ T cells only carried a supply of perforin that had to be replenished by cell proliferation following its release. This method applied for detecting perforin expression to HIV-specific CD8+ T cells [52] has led to important insights into their cytotoxicity potentials in elite controllers, which will be discussed later on in this review.

3. Transcription factors and cytotoxicity of CD8+ T cells

Recent lines of evidence have highlighted the importance of transcription factors and related pathways on cytotoxicity of CD8 + CTLs. However, the underlying transcriptional mechanisms remain elusive for the most part. Numerous transcription factors have been described to play crucial roles in cytotoxic lymphocyte differentiation, and here we discuss a few well-studied ones and their related pathways.

3.1. Eomes and T-bet

T-box transcription factors Eomesodermin (Eomes) and T-bet are probably the most studied transcription factors associated with the cytotoxicity of CD8+ CTLs. These two highly homologous transcription factors coordinately regulate the differentiation of CD8+ effector and memory T cells [53,54]. Loss of both transcription factors skews the phenotype of CD8+ T cells towards IL-17-producing cells [55]. T-bet expression positively controls regulation of genes associated with the effector functions of CTLs such as perforin, Grb2, β-chemokines, and IFN-γ [56]. Moreover, T-bet expression negatively controls regulation of genes hindering the effector functions of CTLs, including IL-2 and PD-1 [56–58]. In terms of HIV-specific CD8+ T cells, it was recently reported that HIV chronic progressors show an imbalance between T-bet and Eomes expression [59]. Most HIV-specific CD8+ T cells are highly skewed towards a T-bet⁺Eomes⁺ profile, while CMV-specific CD8+ T cells from the same donors showed a more balanced expression pattern between the two transcription factors. Importantly, the differential expression pattern between T-bet and Eomes was not reversed despite long-term antiretroviral therapy (ART), and was highly associated with an exhausted phenotype (increased PD-1, CD160, 284 expression and poor effector differentiation), thereby recapitulating the findings from previous studies conducted in mice [60,61].

3.2. Notch proteins

Notch proteins have been reported as single-pass transmembrane receptors that need multiple enzymatic cleavages to create the full-length heterodimer displayed on the cell surface [62]. It has been previously suggested that Notch regulates the expression of the T-box protein, T-bet, in Th1 cells [63]. Notch1 activity mediates CTL activity through direct regulation of Eomes, perforin, and Grb2 [64]. Notch2 partly plays a critical role in the differentiation of CD8+ CTLs whereas it interacts with the promoter of the gene that encodes Grb2 [65]. Recently, Notch has been recognized as an activator for a major portion of the terminal effector cell specific gene-expression program in CD8+ T cells whereas it suppresses the memory precursor cell specific program. Interestingly, expression of Notch was induced on naive CD8+ T cells by inflammatory mediators and IL-2 through a pathway that is dependent on T-bet [66]. HIV Tat has the capacity to interact with the Notch suggesting that such interactions might likely modulate their physiological functions [67].

3.3. Runt-related transcription factor 3

Runt-related transcription factor 3 (Runx3) regulates the expression of Eomes, perforin, GznB and IFN-γ whereas it has been shown that Runx3-deficient CD8+ T cells fail to up-regulate
Eomes, Prf1, Gzmib and Ifng [68]. Runx3 binds to the promoters of Prf1, Gzmib and Ifng in CTLs and up-regulates their product proteins, of which are three cardinal markers of the effector CTL program [68]. Nonetheless, there is no clear evidence on the mechanism by which Runx3 'engineer' the up-regulation of these markers as it could play a likely direct role or act through the induction of Eomes, which can bind to the same promoters [42].

3.4. B lymphocyte-induced maturation protein-1

The B-cell transcriptional repressor B lymphocyte–induced maturation protein-1 (Blimp-1) is an important transcriptional factor implicated in the generation of terminally differentiated plasma cells [69]. Several studies have also demonstrated the role of Blimp-1 as a key factor for the terminal differentiation of effector CD8+ T cells over memory cells [70–72]. The expression of Blimp-1 promotes the over-expression of inhibitory receptors whereas it also suppresses key molecules involved in normal memory CD8+ T-cell differentiation, such as CD62L and IL-7 receptor [73]. Interestingly, high Blimp-1 expression is associated with increased PD-1, CTLA-4, and CD160 expression in chronic HIV infection [60]. Lack of Blimp-1 causes defective cytolytic functions in virus-specific CD8+ T cells and low expression of KLRG1 [74]. Blimp-1 and T-bet appear to have similar roles in promoting the effector functions and terminal differentiation of CD8+ T cells during acute HIV infection [58,75]. Blimp-1 is reportedly crucial for normal perforin and GrB expression and promotes trafficking toward sites of infection by up-regulating CCR5 [71,72].

3.5. Bcl-6

The transcriptional repressor Bcl-6 has emerged as a multifunctional regulator of lymphocyte differentiation and immune responses [76,77]. Bcl-6 has been reported critical for the formation of central memory T cells by induction of IL-10 and IL-21 [78,79]. There is an antagonist role for Bcl-6 against Blimp-1 activity, whereas its expression is associated inversely with Blimp-1 in effector and memory CD8+ T cells [80]. Bcl-6 has also been reported to bind the T-bet promoter and T-bet itself in CD4+ T cells [81–83]. The acquisition of cytotoxic molecules in IL-21-treated CTL has been reported to accompany the sustained expression of Bcl-6, CD27, CD28 and CD62L as characteristic markers of memory T cells [84].

3.6. STAT proteins

Signal transducers and activators of transcription (STATs) proteins are effectors of cytokine signaling in multiple hematopoietic cell lineages that are phosphorylated by Janus kinases (JAKs) in response to proinflammatory and regulatory factors [85–87]. Several studies have shown the significant role of JAK/STAT pathway affecting the pathogenesis of HIV infection [88–91]. Recently, we reported that p38MAPK/STAT3 pathways were involved in HIV-1 mediated up-regulation of inhibitory receptors CTLA-4, TRAIL, TIM-3, LAG-3, CD160 and transcription factors Blimp-1, Dxt1, and Foxp3, as their blockade ameliorated the expression of inhibitory molecules on both CD8+ as well as CD4+ T cells to restore proliferation in vitro [92]. A summary of findings from our recent investigations on the role of CD8+ and CD4+ T-cell regulation has been shown in Fig. 1 (and has also been extensively reviewed [72]). A previous in vitro study, using CD8+ T cells from healthy donors infected with HIV-1, it was shown that concurrent signaling via IL-15 and IL-21 partially alleviated the immunosuppressive effects of HIV-1 on granulysin expression through STAT3/STAT5 signaling [93]. STAT3-mediated signals have been suggested to support a TCR-initiated gene expression program for differentiation of effector CD8+ T cells [94]. Binding of Eomes and STAT5 to Prf1 cis-regulatory regions correlate with transcriptional initiation of Prf1 by increasing the recruitment of RNA polymerase II to its promoter [79].

4. Immunosenescence and co-inhibitory molecules

HIV-specific CD8+ T cells express similar levels of CD38 and HLA-DR, which correlate with viral load in non-controllers [95]. High frequency of CD38+/HLA-DR+ HIV-specific CD8+ T cells has been reported in HIV controller [96,97]. A subset of these activation markers have been also reported to have a higher frequency of polyfunctional cells, and higher proliferative and cytotoxic capacities than the CD38+/HLA-DR- subset [98]. Measurement of immune activation markers on T cells in regards to vaccine responses is important given the concerns of generalized immune activation, especially with adenovirus platforms [99].

The α chain of the IL-7 receptor (IL-7R, also called CD127) has been suggested to selectively characterize CD8+ T cells that will become long-lived memory cells [100–102]. Furthermore, it was shown in humans [103–105] that the CD127high memory-precursor CD8+ T cells produced IL-2 in contrast to CD127low effector CD8+ T cells. CD127 expression by HIV-specific CD8+ T cells is low in both early and chronic HIV infection, and this is associated with viral replication and immune activation [104], [106–108]. On the other hand, CD127 expression on virus-specific CD8+ T cells is correlated positively with proliferation capacity and negatively with perforin expression and cytotoxicity [109]. High T-bet expression promotes terminally differentiated CD127hi KLRG-1low effector CD8+ T cells and sustains functional virus-specific CD8+ T-cell responses [58].

Functional heterogeneity has recently been reported among CD57+ cytotoxic T cells including terminally differentiated, highly cytotoxic EomeshiCD57+CD8+ T cells and less differentiated EomesloCD57+ CD8+ T cells with high proliferative capacity and interleukin 7 (IL-7) receptor expressions. HIV controllers in this study showed a high proportion of Eomeshi CD8+ T cells among CD57-expressing HIV-specific CD8+ T cells compared to aviremic antiretroviral-treated patients and viremic patients, demonstrating a unusual phenotype that potentially could be linked to effector mechanisms and viral control [110].

CD56, or neural cell adhesion molecule-1 (NCAM-1), is a cell surface glycoprotein present on NK and T cells. CD56 expression identifies the subset of CD8+ T cells most potent for cytotoxicity [111–113] probably due to higher cellular content of perforin and GrB. Higher levels of the anti-apoptotic protein Bcl-2 has been observed in CD56 expressing cells, which are mostly long-lived, effector memory cells [114,115]. Interestingly, higher perforin upregulation as well as degradation has been reported in HIV Gag-specific CD8+ T cells expressing CD56 compared with CD56-HIV Gag-specific CD8+ T cells [115].

4.1. TIM-3

TIM-3 belongs to the TIM family of molecules, and TIM-1 through TIM-8 reportedly exist in mice, whereas humans express only TIM-1, TIM-3, and TIM-4. TIM-3 expression is elevated on CD4+ and CD8+ T cells during chronic HIV infection [116–118] and once ligated to its ligand, Gal-9, it induces T-cell suppression [73]. Poonia and Pauza observed high levels of TIM-3 on CD56+ CD8+ T cells of ART-treated HIV patients, implying that defective effector function was related to immune exhaustion. Interestingly, elite controllers had the highest frequencies of perforin producing CD56+ CD8+ T cells among all HIV+ groups, whereas CD56+ CD8+ T cells from elite or treated HIV patients expressed T-bet and Eomes.
at levels similar to uninfected controls after stimulation with PMA plus ionomycin [115]. A recent study revealed that defect in effector lytic activity is largely attributed to irreversible immune exhaustion and quantitative loss of CD56+ CD8+ T cells, which is not even repaired in ART-treated patients with suppressed HIV vir-emia and CD4+ T-cell recovery. It has recently been shown that TIM-3 expression is dependent on the Type 1 helper T (Th1) and Type I CD8+ cytotoxic T (Tc1) transcription factor T-bet [119]. On the other hand, T-bet is essential for normal production of perforin and functioning of cytotoxic lymphocytes [119–122]. TIM-3+ CD8+ T cells has been reported to express high levels of perforin and T-bet as shown in HIV studies whereas these cells were mainly in a granule-associated (stored) conformation, as well as defective in their ability to degranulate [118]. In a recent study, it was shown that blockade of TIM-3 signaling pathway enhanced the cytotoxic potentials of CD8+ T cells in chronic progressors, which was very close to that of T cells of viral controllers. Therefore, TIM-3 acts not only as a terminator of cytokine production and proliferation in CTLs, but also as a factor that can cause attrition of cytotoxic abilities of CD8+ T cells via inhibition of degranulation, and secretion of perforin and granzyme [118].

5. Immunoregulatory cytokines

5.1. IL-2

IL-2 concurrently up-regulates Eomes and Runx-3 whereas IL-21 only induces Eomes, suggesting that these two cytokines control perforin and GrB transcription in CD8+ T cells, at least in part, through distinct mechanisms [84]. However, IL-2 promotes lower accumulation of perforin and GrB at the protein level through mRNA expression of GzB and PRF1 in comparison with IL-21 [84]. IL-2 stimulation induces the Eomes, upregulated Prf1 transcription, and represses re-expression of Bcl-6 and IL-7Rx [79].

5.2. IL-21

IL-21 is a member of the cytokine family which shares the common gamma chain (γc) (or CD132) in their receptor complexes including IL-2, IL-4, IL-7, IL-9, and IL-15 [123–125]. White et al. demonstrated the role of IL-21 in enhancing perforin expression preferentially in CTL from HIV-infected individuals which arises an interest in investigating IL-21 in the context of HIV infection [126]. IL-21 plasma levels has been reported to reduce in HIV-infected individuals and ART only partly improve this defect [127]. Intriguingly, it has demonstrated that IL-21 induces cytotoxic function without CD4+ T or CD8+ cell activation or HIV replication leading to consider it as a potential immunotherapy treatment [84,127]. Recent study has also reported potential role of IL-21 to enhance cytotoxic activity of CD8+ T cells by up-regulating perforin and GrB without augmentation of PD-1 expression [84]. IL-21 production in CD4+ T cells which indirectly leads to the development of GrB-secreting B cells with antiretroviral properties [128]. IL-21 production by CD4+ T cells of HIV controllers increases perforin production by HIV-1-specific CD8+ T cells from chronic progressors even in late stages of disease, and HIV-1-specific effector CD8+ T cells have enhanced capability to efficiently inhibit viral replication in vitro after IL-21 binding [129].

6. Cytotoxic CD8+ T cells in long-term non-progressors and elite controllers

HIV-specific CD8+ T cells probably mediate control over virus replication in rare individuals, termed long-term non-progressors (LTNPs) or elite controllers [130]. There have been reports demonstrating many cell surface markers, activation profiles, and functional parameters of both ex vivo HIV-specific CD8+ and CD4+ T cells that correlate with control of viremia [131–134] although a few of them can potentially mediate direct control of virus
replication through the lysis of infected cells [96]. Efficacious cytotoxic functions is beneficial for HIV-infected individuals, because CTL from HIV controllers have a higher capability to eliminate HIV-infected CD4+ T cells as compared to CTL from progressors [130]. HIV-specific CD8+ T cells from elite controllers synthesize greater amounts of cytotoxic granule components, which enable greater cytotoxic function synergistically inducing apoptosis in target cells [52,130,135]. The increased expression of these cytotoxic granule components appears to be partially under the control of T-bet that can directly bind to the promoter regions of perforin and GrB genes and that seems to be exceptionally up-regulated in HIV-1-specific T cells from elite controllers [120,136]. LTNPs possess HIV-specific CD8+ CTLs restricted by HLA-B*27 or HLA-B*57 that can continue to proliferate throughout chronic infection, whereas the majority of HIV-specific CD8+ CTLs restricted by other HLA alleles lose their proliferative capacity [45,137,138]. Proliferative capacity is linked to up-regulation of perforin and is, therefore, associated with the cytotoxic capabilities of virus-specific CD8+ CTLs [45].

Migueles et al. has reported that HIV-specific CD8+ CTLs restricted by the protective HLA allele groups (HLA-B*27 and HLA-B*57) up-regulate more GzmB than HIV-specific CD8+ CTLs restricted by other HLAs. This up-regulation is independent of their enhanced proliferative activity. These HIV-specific CD8+ CTLs of LTNP’s restricted by HLA-B*27 and HLA-B*57 alleles have an extraordinary cytotoxic ability to eliminate HIV-infected CD4+ T cells on a per-cell basis. This function was mediated by lytic granule loading of effectors and delivery of GzmB to target cells [130]. Furthermore, a recent study showed that CD8+ effectors that express high amounts of GzmB escape Treg cell-mediated suppression by killing Treg cells that they encounter [139]. Elahi et al. showed that HLA-B*27- and HLA-B*57-restricted effectors escape Treg cell-mediated suppression by directly killing Treg cells whenever they encounter them in a GzmB-dependent manner [140]. Treg cells express galectin-9, which is a ligand for TIM-3, an inhibitory molecule found on effector T cells. Elahi and his colleagues also described that Treg cells suppress proliferation of non-protective HIV-specific CD8+ CTLs through interaction of TIM-3 with its corresponding ligand Gal-9 during chronic infection whereas Treg cells do not block proliferation of HIV-specific CD8+ CTLs that recognize antigens presented by restricted by mentioned protective HLA allele groups [140].

HIV-specific CD8+ CTLs restricted by the protective HLA allele groups can resist Treggs suppression and subsequently keep their proliferative capacity and cytotoxicity by two ways. They have the ability to directly kill Treg cells. On the other hand, they can down regulate TIM-3 expression on their surface avoiding the exhaustion through Gal-9-TIM3 interaction by Tregs [140]. Recently, there is an interesting report that HIV controllers have a high proportion of exhausted (PD1+ CD160+ 2B4+) HIV-specific CD8+ T-cells comparable to that observed in chronic progressors [141]. It will be crucial to assess the degree of exhaustion that inhibitory receptors exert on CD8+ T-cell functions most critical for HIV control/prevention, and to consider this impact on a candidate HIV vaccine [99].

An increasing number of reports have suggested that CD4+ T-cells can themselves display potent antiviral activity by directly killing virally infected cells [26,28,142]. Moreover, CD4+ T cells from HIV-infected patients have been identified to express large amounts of cytolytic effector molecules, and HIV-specific CD4+ T cells can mediate lysis of target cells and viral inhibition in vitro [27,143,144]. Sohphoan et al. has reported that individuals capable to spontaneously control HIV replication in the absence of antiretroviral therapy showed a meaningful expansion of HIV-specific CD4+ T cell responses compared to individuals who progressed to a high viral set point prior to differences in viral load or CD4+ T cell count [145]. These subjects showed a much larger fraction of HIV-specific CD4+ T cells that carried granules containing granzyme A whereas high granzyme A levels in HIV-specific CD4+ T cells is associated with about a one-year delay in the onset of disease progression [145].

Previous reports have examined perforin expression in HIV-specific CD8+ T-cells in both progressive and nonprogressive infection [44,138,146]. However, these studies have uniformly defined only the level of pre-formed, granule-associated perforin present within resting or long-term activated HIV-specific CD8+ T-cells due to unforeseen limitations in the anti-perforin antibody employed in these studies [13,147]. Hersperger et al. have observed that HIV-specific CD8+ T cells from non-progressors, compared to progressors, have a superior ability to express perforin immediately upon activation, without the need for prior proliferation or the addition of exogenous cytokines [52]. This study also indicates that this ability is not restricted to protective HLA-B haplotypes, is not restored by HAART, and primarily originates from effector CD8+ T-cells with otherwise limited functional capability. They also found a significant inverse correlation between the average perforin expression in CD8+ T cells and HIV viral load.

7. Boosting the immunity of cytotoxic CD8+ T cells to inhibit viral replication

Boosting the cytotoxic credentials of CD8+ T cells is key to control of HIV replication. Stephen and others have reported that the proliferative and cytotoxic functions of HIV-specific CD8+ T cells are seldom restored by antiretroviral therapy [148]. The antiviral inhibitory capacity of CD8+ T cells is highly predictive of the rate of CD4+ T-cell decline in HIV disease [149]. This suggests that CD8+ T cell viral inhibitory activity is expressed on a continuum and is not a discrete function that is unique to HIV controllers with protective HLA alleles. Therefore, this finding has potential as a benchmark of effective immunity in vaccine evaluation for induction of effective CD8+ T cell responses by vaccination of individuals who do not have a ‘favorable’ genotype [150,151]. An HIV-1 vaccine candidate, consisting of DNA and recombinant adeno-virus type 5 (rAd5) vectors was tested in a phase I clinical trial, which resulted in the induction of CD8+ T cells that efficiently inhibited HIV-1 in a HLA-I-dependent manner [152]. Researchers from Tomaras lab also found that a multiclade DNA prime/recombinant rAd5 boost vaccine elicited CD8+ T cells with antiviral activity. In chronically infected virus controllers, this activity was best associated with HIV-1-specific CD107a or macrophage inflammatory protein 1β (MIP-1β) expression from HIV-1-specific T cells [51]. A prophylactic T-cell based HIV vaccine must induce a response able to clear virally infected cells; it follows then that there is a need to assess HIV-specific cytotoxicity as a primary function of vaccine-induced CD8+ T cells [98]. Besides, this is essential to generate an immunological portfolio for the evaluation of vaccine efficacy, with consideration of perforin expression being amongst the foremost criteria for success.

8. Conclusion

Our understanding of the complex nature of regulatory mechanisms leading to effective CD8+ CTL immune responses against HIV is still far from complete, and therefore therapeutic attributes that aim to improve protective CTL responses to target transcriptional factors that can harness such responses are urgently warranted through understanding of the different factors that control such immune responses. Clear insights into the regulation of cytotoxic CD8+ T cells, is crucial to provide effective immunotherapeutic strategies due to their unique ability to eliminate virus-infected cells in HIV disease.


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