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Kill: Boosting HIV-specific immune responses

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Abstract

Purpose of review—Increasing evidences suggest that purging the latent HIV reservoir in virally-suppressed individuals will require both the induction of viral replication from its latent state and the elimination of these reactivated HIV infected cells ("Shock and Kill" strategy). Boosting potent HIV-specific CD8 T cells is a promising way to achieve an HIV cure.

Recent findings—Recent studies provided the rationale for developing immune interventions to increase the numbers, function and location of HIV-specific CD8 T cells to purge HIV reservoirs. Multiple approaches are being evaluated including very early suppression of HIV replication in acute infection, adoptive cell transfer, therapeutic vaccination or use of immunomodulatory molecules. New assays to measure the killing and antiviral function of induced HIV-specific CD8 T cells have been developed to assess the efficacy of these new approaches. The strategies combining HIV reactivation and immunobased therapies to boost HIV-specific CD8 T cells can be tested in *in vivo* and *in silico* models to accelerate the design of new clinical trials.

Summary—New immunobased strategies are explored to boost HIV-specific CD8 T cells able to purge the HIV-infected cells with the ultimate goal of achieving spontaneous control of viral replication without antiretroviral treatment.

Keywords

HIV-specific CD8 T cells; immunobased therapies; post-treatment control of HIV replication

Introduction

Despite the success of antiretroviral therapy (ART) in controlling HIV replication, ART does not eradicate HIV and does not optimally reconstitute the immune system (1, 2). Novel immunobased therapies that would induce the immune-mediated control of HIV replication in the absence of ART or the eradication of the HIV reservoir are needed. To date, a single case of HIV cure and rare cases of transient remission have been reported (3–8). Other few reported cases of long-term remission in individuals controlling viral replication after ART interruption, also called "post-treatment controllers", have been documented (9–13).

Conflicts of interest

The author declares no conflict of interest.

However for most HIV-infected individuals, HIV viral load rebounds at a median time of 14 days after treatment interruption from a large number of HIV variants (14–16). Inducing HIV expression has been proposed as a strategy to eliminate persistently HIV-infected cells that constitute the viral reservoir (17–19). Latency reversing agents (LRAs) with potential for viral induction have been identified in *in vitro* models of HIV latency (20, 21) and are discussed in reviews on "shock" strategies in this issue. Despite their ability to induce HIV production, LRAs did not induce measurable decrease of the HIV reservoir size *in vivo* (22–25). Therefore, purging these latent HIV reservoirs remaining under ART will need in addition to the induction of viral expression (Shock), the elimination of these reactivated latently-infected cells by either direct cytolytic targeting or by immunotherapeutic intervention (Kill) (26). Whereas rapid progress is made on the discovery and characterization of new LRAs to reactivate the latent HIV reservoir, the critical issue of how to kill the reactivated cells has still to be defined. In this review, the recent advances in using HIV-specific CD8 T cells to purge the latent HIV reservoir and achieve viral control after ART interruption will be discussed.

The need for efficient HIV-specific CD8 T cells to purge the HIV reservoir

Several observations suggest that HIV-specific CD8 T cells are important for the control of HIV replication by killing the productively HIV-infected CD4 T cells including the generation and maintenance of viral escape mutations in CD8 T cell epitopes or the superior control of viral replication by certain HIV-specific clonotypes restricted by HLA-B57 and B27 in elite controllers (27–29). The critical role of CD8 T cells in controlling HIV reservoir in virally-suppressed conditions has been demonstrated in the SIV model, where CD8 T cell depletion led to a rapid increase in viremia in elite controller macaques (30, 31) but also in virally suppressed ART-treated macaques (32). In both cases, the recovery of CD8 T cells after depletion was associated with a reduction of viral production. However, HIV-specific CD8 T cell mediated control of HIV replication is not sufficient to purge the HIV reservoir and prevent viral load rebound after ART interruption. Several parameters contribute to the lack of viral reservoir clearance by HIV-specific CD8 T cells. Prior to ART, many studies have shown that HIV-specific CD8 T cells are dysfunctional and have characterized the mechanisms of this dysfunction (33–36). After ART initiation, these defects are not fully restored and the remaining number of HIV-specific CD8 T cells is extremely low due to the sharp decrease of antigen load and continues to decay over time (37–42). Additionally, viral escape in epitopes targeted by CD8 T cells emerging rapidly early in infection as well as viral mechanisms interfering with the presentation of viral antigens prevent CD8 T cells to recognize efficiently HIV-infected cells. Lastly, the compartmentalization of HIV-infected cells in B cell follicles hardly accessible to HIV-specific CD8 T cells adds another barrier to efficient killing of these cells (31, 43, 44). The low frequency of HIV-specific CD8 T cells, their partial dysfunction and their location outside of HIV reservoir sanctuaries may account for the failure of previous eradication strategies that have been implemented in HIV-infected individuals who have been receiving ART for years.

Recent studies suggested that HIV-specific CD8 T cell could play an important role in purging HIV reservoirs. Shan and colleagues reported that after *in vitro* expansion of HIV-specific CD8 T cells from ART-treated subjects, these cells were able to eliminate

reactivated HIV-infected CD4 T cells in an *in vitro* model of latency (45). Hansen and colleagues developed a new RhesusCMV vaccine that induced high frequencies of potent SIV-specific CD8 T cells leading to viral control and complete elimination of SIV reservoirs in half of the vaccinated macaques (46, 47). The high frequencies of SIV-specific CD8 T cells induced by this therapeutic vaccine were directed against broad non-classical epitopes restricted by HLA-E suggesting that immunobased strategies boosting HIV-specific CD8 T cells need to induce more efficient responses than the ones occurring in natural infection (48, 49). CD8 T cell responses restricted by HLA-E have been documented in infectious diseases, cancer and autoimmunity but have been mostly characterized as regulatory responses (50–52). Whether HIV-specific CD8 T cells responses against HLA-E restricted epitopes will be defined as important in controlling HIV replication and can be induced in human is still unknown but is under investigation. These studies provided the rationale for new therapeutic strategies that combine agents that reactivate latently-infected CD4 T cells with immune interventions that increase the numbers, function and location of HIV-specific CD8 T cells to clear HIV reservoirs in individuals on ART, with the ultimate goal of achieving spontaneous control of viral replication without treatment (53).

Strategies to boost HIV-specific CD8 T cell responses in ART-treated subjects

Different approaches are currently tested to boost HIV-specific CD8 T cells in ART-treated individuals and are described below.

1- Initiating ART in acute infection

Although the latent HIV reservoir is seeded very early in infection (54, 55), initiating ART as early as possible can limit the size of the viral reservoir and could also preserve the quality of HIV-specific responses (56–63). Whether a preserved immunity could lead to the control of viral replication after treatment cessation remains largely unknown but two studies initiated ART in primary infection and assessed the viral rebound after ART discontinuation. In the SPARTAC study, treatment initiation within 6 months of infection resulted in a delay in viral rebound after ART cessation (64, 65). Hurst and colleagues reported recently that immune checkpoint blockers PD-1, Tim-3 and Lag-3 measured prior to ART initiation strongly predicted time to viral rebound after ART cessation (66). In the VISCONTI cohort, treatment was initiated within the first 3 months of infection and kept for a median of 7 years before ART cessation; fourteen post-treatment controllers were observed in that cohort (11). These two studies suggest that timely ART initiation may pave the way for a better viral control after ART cessation but the mechanism of viral control in post-treatment controller still needs to be identified (67). Early in infection, HIV-specific CD8 T cells can contribute to control viremia (68–71) but become rapidly dysfunctional after peak viremia due to sustained hyperactivation and change in their metabolism (72). Therefore, initiating ART in the earliest stage of acute infection before peak viremia is reached might be necessary to achieve HIV remission due to initiating ART early in infection. This will be answered in ongoing or planned clinical studies.

2- Adoptive transfer of ex vivo expanded HIV-specific CD8 T cells

Early studies in the SIV model described adoptive transfer of CD8 T cells in acute and chronic untreated infection with limited impact on viral replication (73–75). However the impact of adoptive SIV-specific CD8 T cell transfer on the SIV reservoir under suppressed viremia before treatment interruption remains to be tested. Recently, Sung and colleagues demonstrated that *ex vivo* expanded CD8 T cells derived from ART-treated HIV-infected individuals controlled the autologous viral reservoir better than bulk CD8 T cells, supporting the use of adoptive CD8 T cell transfer for purging the HIV reservoir *in vivo* 76). Emerging findings from adoptive CD8 T cell transfer approaches tested in cancer both in mouse studies and clinical trials show promising results and indicate that intrinsic properties related to the differentiation state of the adoptively transferred CD8 T cells are crucial for the success of these approaches (77). Chapuis and colleagues demonstrated that HIV-specific CD8 T cells expanded *in vitro* from the central memory pool of ART-treated individuals were detected more than 84 days *in vivo* after re-injection (78). However, the mechanisms that underlie successful adoptive CD8 T cell transfer in HIV-infected ART-treated individuals remain unknown and the most effective T cell populations to kill HIV reservoir cells *in vivo* have yet to be identified.

3- Therapeutic vaccines

Over the last decade, many T cell based vaccine regimen have been tested to boost CD8 T cell responses (reviewed in (79)). Live attenuated vectors have been favored as they induce robust CD8 T cell responses but other vaccination strategies using peptides, proteins, or dendritic cells have been tested in HIV-infected individuals on ART. These therapeutic vaccines tested showed limited success in delaying viral rebound after cessation of ART but lessons can be learned from these therapeutic vaccination studies (reviewed in (80)) and new therapeutic vaccines show promising results (reviewed in (81)). One of the reasons for the limited success of therapeutic vaccines tested in clinical trials so far might be that these interventions have been designed following classical vaccine regimen for inducing memory T cells. The boosting of HIV-specific CD8 T cells through therapeutic vaccination should aim at inducing numerous, potent, broad effector CD8 T cells (82). Defining the correlates of vaccine efficacy for achieving HIV remission after treatment interruption would help guiding the development of successful therapeutic vaccines.

4- Immunomodulators

Immunomodulation strategies aim at potentiating HIV-specific CD8 T cells either endogenous or induced by vaccines to kill reactivated HIV-infected cells. Some of the strategies currently tested *ex vivo* and in clinical trials to reactivate HIV from latently-infected CD4 T cells target signaling pathways associated with T cell activation and homeostasis, including PKC activators, as Bryostatin or Ingenol, and cytokines, as IL-7 (83, 84). Besides their effect on the latent HIV reservoir, these molecules could also influence differentially the activation and function of HIV-specific CD8 T cell responses stimulated contemporaneously. Vaccine adjuvants can also play a dual role of reactivating the latent reservoir and enhancing vaccine responses. Agonist molecules targeting TLR7 and TLR9 have been shown to reactivate the HIV reservoir (85, 86). Finally, the success of monoclonal

antibodies targeting immune checkpoint blockers in cancer treatment could be transposed to HIV eradication. A recent clinical trial blocking the PD-1/PD-L1 pathway in ART-suppressed individuals suggested that this treatment could revert the immune exhaustion of HIV-specific CD8 T cells while enhancing HIV expression in CD4 T cells (87).

Although some of these different strategies explored to boost HIV-specific CD8 T cells would not be applicable to all HIV-infected individuals, they are critical in defining the characteristics of efficient HIV-specific CD8 T cells that could control viral rebound after ART cessation and will guide the development of novel therapeutic approaches.

Assays to measure the number, location and killing capacity of HIV-specific CD8 T cells

The different approaches currently tested to boost HIV-specific CD8 T cells in ART-treated individuals described above will require specific assessments of the CD8 T cells induced: their number; but also their ability to persist in vivo; the location of these cells in particular in sanctuary sites of viral persistence; and their capacity to kill reactivated latently-infected CD4 T cells.

1- Quantify the numbers and maintenance of HIV-specific CD8 T cells during immune intervention and ART interruption

The frequencies of HIV-specific CD8 T cells are very low in the peripheral blood of ART-treated individuals and are difficult to detect using standard assays such as ELISPOT or *ex vivo* ICS. Furthermore, the repeated sampling of subjects undergoing immune intervention and analytical treatment interruption limits the number of cells available to analyze these low frequencies. The same limitations exist for the measurement of HIV reservoir under ART and have led to the development of ultrasensitive methods for viral detection. Similarly, ultrasensitive methods to detect HIV-specific CD8 T cells accurately under ART should be developed and validated.

2- Assess the location of HIV-specific CD8 T cells

Immunohistochemistry allows the visualization of T cell localization in tissues. The detection of CD8 T cells in paraffin embedded tissues is not optimal yet but will be necessary to localize the CD8 T cells in mucosal tissues or secondary lymphoid organs. The detection of HIV-specific CD8 T cells in tissues can be done by in situ tetramer staining (88), a powerful but difficult method that might not be widely available in many laboratories and requires the staining of tissues from individuals having HLA alleles matching available tetramers. Alternatively, defining markers on HIV-specific CD8 T cells that are representative of the CD8 cells location in specific tissues and can be measured on dissociated tissues by flow cytometry would facilitate the assessment of HIV-specific CD8 T cell localization in tissues.

3- Measure the killing capacity of HIV-specific CD8 T cells

The cytolytic activity is the major function of CD8 T cells required for the elimination of HIV-infected cells but is still rarely evaluated, as assays used for this purpose are

cumbersome, cell consuming and have been difficult to standardize. Accurate measurement of this function is of paramount importance when characterizing effector functions of CD8 T cells, as no reliable predictors of effective cell-mediated cytotoxicity have been described yet (89, 90). Using a new assay to quantify the intrinsic killing capacity of HIV-specific CD8 T cells, we have observed that HIV-specific CD8 T cells in primary infection exhibit a significantly higher cytotoxic capacity than HIV-specific CD8 T cells in chronic infection (72, 91, 92). A new assay measuring the antiviral activity of CD8 T cells has been recently developed using *in vitro* infected CD4 T cells co-cultured with CD8 T cells (45, 93–95). Using this assay, Yang et al. demonstrated a significant association between CD8 T cell viral inhibition activity *in vitro* and the rate of CD4 T cell loss in early HIV-1 infection as well as the rate of CD4 T cell decline in chronically infected individuals (96). Whether this viral inhibition is mediated by direct cytolytic activity of CD8 T cells is still unknown and other assays that can recapitulate the killing of primary latently-infected CD4 T cells from ART-treated individuals by HIV-specific CD8 T cells need to be developed.

New assays requiring limited PBMCs that measure small frequencies of HIV-specific CD8 T cells while assessing their quality, location and ability to kill HIV-infected cells would be an important platform to test the immune intervention strategies for HIV reservoir eradication in ART-treated individuals.

In vivo and *in silico* models to test therapeutic immune interventions

New immune interventions will be tested in clinical trials in the coming years using combination strategies to reactivate HIV reservoir and boost HIV-specific CD8 T cells in order to eradicate HIV. In designing these new therapies combining multiple components, it will be critical to understand the effect of the drugs used for HIV reactivation on HIV-specific CD8 T cells and to determine the timing of administration of these therapies. Indeed, current LRAs have been shown to inhibit HIV-specific CD8 T cell responses *in vitro* 97), so the timing of administration of these LRAs and vaccine regimen needs to be carefully chosen to avoid these deleterious effects on CD8 T cells. *In vivo* effects of the different combinations of LRAs and immunobased interventions will be difficult to predict and calls for models to anticipate the outcome and accelerate the testing of combination strategies. In the recent years, the antiretroviral regimens have been optimized in SIV-infected macaques and allow for viral suppression (see review on “animal models for eradication strategies” in this issue). Therefore, the non-human primate model can be used for testing of new vaccine regimen or immune intervention and drug combinations. This model also allows for a deeper examination of HIV reservoirs and HIV-specific CD8 T cells in tissues that would not be accessible in human.

In addition, mathematical modeling is essential to inform novel combination strategies. *In silico* models have provided accurate and useful information on viral dynamics (98–101) and have already been used to model post-treatment control. A recent study modeled the dynamics between viral reactivation and control by the immune response after ART interruption and predicted the time to relapse in individuals treated in primary infection (102). Smith and colleagues used *in vivo, in vitro* and *in silico* data to model the control of viral rebound by CD8 T cells post-transplantation in an HIV autologous elite controller that

underwent stem cell transplantation (103). In another study, based on previous clinical trial with analytical treatment interruption, Pinkevych and colleagues estimated the rate of successful reactivation after ART cessation to be once every 3.6 days (104). For the immune response to HIV, even though data are available on the *in vivo* killing rate of infected cells by CD8 T cells (105), few *in silico* models are available to predict the number and nature of CD8 T cells required for HIV remission. However, a recent study modeled the timing of LRA administration and suggested that reactivation of the latent reservoir could be more effective at start of ART rather than on long term ART, when HIV-specific CD8 T cells are still present in high numbers (106). The use of combination strategies will introduce more variables and increase considerably the complexity of these models. Data from clinical trials including analytical treatment interruption will help building and refining the mathematical models of post-treatment control, which will then guide the next trials. This iterative process should accelerate the pace of testing successful immune interventions to eradicate HIV.

Conclusion

Despite major advances in defining the mechanisms of HIV latency and its reactivation using different strategies (107, 108), the “Kill” part of the “Shock and Kill” strategy has to be defined in the clinical setting. Evidences from the RhCMV vaccine and *in vitro* data show that superior HIV-specific CD8 T cells need to be induced by immune intervention in order to eradicate HIV infected cells. Several strategies are tested to boost these responses but whether HIV-specific CD8 T cells need to be boosted numerically and/or qualitatively and to which extent are still open questions. Numerous trials will be performed in the next few years and new assays measuring the quality and effector function of the HIV-specific CD8 T cells induced will be important to evaluate these interventions. *In vivo* and *in silico* models for testing novel combination strategies aiming at reactivating the HIV reservoir and boosting HIV-specific CD8 T cells will accelerate the pace of human clinical trials. In all these immunobased strategies, timing of intervention might play an important role in the outcome and should be carefully assessed. It is possible that potent immune interventions to boost HIV-specific CD8 T cells would also induce HIV reactivation and would be sufficient to eliminate HIV reservoirs (109, 110). In that case, a “Purge” strategy aiming at the elimination of HIV-infected cells by boosting HIV-specific CD8 T cell killing could lead to HIV eradication. Finally, defining immunological predictors of post-treatment control will be critical to guide the development of immune-based therapies to achieve HIV remission after ART cessation.

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Key points

Recent studies provide the rational to develop strategies to boost HIV-specific CD8 T cells to achieve an HIV cure.

Boosting HIV-specific CD8 T cells could be achieved by early ART initiation, adoptive cell transfer, therapeutic vaccination and immunoregulatory interventions.

New immunological assays to assess the number, quality and effector functions of HIV-specific CD8 T cells should be used to assess immune-based therapies.

In vivo and *in silico* models can guide the development of combinations strategies to boost HIV-specific CD8 T cells in combination with intervention to reactivate the latent HIV reservoir.