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Programming T cell Killers for an HIV Cure: Teach the New Dogs New Tricks and Let the Sleeping Dogs Lie

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Abstract

Despite the success of combination antiretroviral therapy (cART), a latent viral reservoir persists in HIV-1-infected persons. Unfortunately, endogenous cytotoxic T lymphocytes (CTLs) are unable to control viral rebound when patients are removed from cART. A “kick and kill” strategy has been proposed to eradicate this reservoir, whereby infected T cells are induced to express viral proteins via latency-inducing drugs followed by their elimination by CTLs. It has yet to be determined if stimulation of existing HIV-1-specific CTL will be sufficient, or if new CTLs should be primed from naïve T cells. In this review, we propose that dendritic cells (DCs), the most potent antigen presenting cells, act as dog trainers and can induce T cells (the dogs) to do magnificent tricks. We propose the hypothesis that an HIV-1 cure will require targeting of naïve T cells and will necessitate “teaching new dogs new tricks” while avoiding activation of potentially dysfunctional endogenous memory CTLs (letting the sleeping dogs lie).

Keywords

CTL; dendritic cells; HIV-1; immunotherapy

I. INTRODUCTION

Combination antiretroviral therapy (cART) has greatly reduced the morbidity and mortality associated with chronic HIV-1 infection. While on cART, subjects experience partial CD4⁺ T cell recovery and decreases in AIDS-defining opportunistic infections, and many maintain plasma viremia at levels undetectable by standard assays (<50 copies/ml).¹ Despite this, viral reservoirs persist in the gut-associated lymphoid tissues and other lymphatics and blood.^{2–4} Importantly, the frequency of anti-HIV-1 CD4⁺ and CD8⁺ T cells decreases, presumably due to low antigenic stimulation consequent to the lower viral load.^{5–7} Thus, partial immune reconstitution is achieved during cART, but the functionality of the reconstituted immune system is limited.⁸ When subjects are removed from cART, due to

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drug toxicity or treatment noncompliance, there is an associated rebound in HIV-1 load and resumption of disease progression.^{4,9}

T cell immunity is the most important parameter in controlling virus infection in the absence of cART and is paramount in controlling virus infection in concert with cART.^{10–13} Hence, to effectively control HIV-1 replication and ultimately cure HIV-1 infection, a “shock” or “kick and kill” approach has been proposed.¹⁴ In this model, latently infected CD4⁺ T cells are induced (the “shock”) to produce viral protein antigens, together with a potent immunotherapy that induces cytotoxic T lymphocytes (CTLs) specific for the patient’s own, unique (autologous) virus (the “kill”). We use the analogy in this commentary of these T cells being immune “police dogs” that need to be trained to do unique and spectacular tricks.

II. THE PROFESSIONAL DOG TRAINERS—MYELOID DENDRITIC CELLS (DCS)

We and others propose that the afferent arm of the killer response can be induced by autologous dendritic cells (DCs),^{15–19} the most potent antigen-presenting cells (APCs), which are capable of enhancing the breadth, magnitude, and polyfunctionality of the efferent or effector arm of the immune response, i.e., HIV-1-specific CTL responses.^{20–24} Critical features of this approach and the rationale behind using DCs as an HIV immunotherapy has been described elsewhere.¹⁵ A key issue in this approach is how these DCs are educated to result in the greatest breadth and magnitude of anti-HIV-1 T cell reactivity after they are given as an immunotherapy. During cART, myeloid DCs obtained from blood monocytes and matured with mixtures of different cytokines and T cell co-stimulatory molecules retain their capacity to process and present antigen^{25,26} and stimulate HIV-1-specific IFN- γ production in CD8⁺ (Refs. 21, 27, 28) and CD4⁺ T cells.²⁹ In particular, we have shown that DCs generated from subjects on cART have the capacity to secrete high levels of IL-12p70 if treated with the combination of CD40L and IFN- γ , or the α DC1 maturation cocktail that is being used in cancer immunotherapy trials.^{21,30,31} This supports the functional integrity of DCs in HIV-1-infected persons on cART, and underscores their usefulness in immunotherapy. Other critical factors in this afferent arm of the DC immunotherapy model are the type/dose of HIV-1 antigen, dose of DCs, route of inoculation, and other immunological parameters as previously discussed.¹⁵

III. TEACHING THE NEW DOGS NEW TRICKS

A major consideration in the immunotherapy approach we propose is which subset or subsets of T cells should be the target of activation by HIV-1 antigen-loaded DCs to achieve an optimal antiviral response. We propose that the key objective of a DC-based immunotherapy to treat HIV-1 infection should be to specifically target naïve T cell precursors in order to prime CTLs *de novo* (teach the new dogs new tricks), and avoid or even inhibit activation of the existing, dysfunctional memory T cell population (let the sleeping dogs lie), as their presence prior to cART^{32,33} already supports the notion that they are incapable of controlling the virus. This is problematic, however, as studies have revealed decreases in the prevalence and function of naïve T cells following HIV-1 infection compared to uninfected controls.^{34–37}

Abnormalities in T cell receptor (TCR) diversity and function, including responsiveness to neo-antigens, have also been reported in chronic HIV-1 infection and are reviewed elsewhere.³⁸ It has been suggested that the pool of naïve T cells present in long-term, HIV-1 chronically infected subjects on cART may not have a sufficient TCR repertoire or functional capacity to respond to primary stimulation against autologous HIV-1,^{34–37} or that viral escape has specifically evaded potential recognition by this new repertoire of naïve T cells.^{39–41} Moreover, alterations in T cell homeostasis during chronic, untreated HIV-1 infection largely impact the naïve subset and partially result from decreases in thymic output.^{36,37,42} Under cART, however, there is a progressive restoration of naïve CD4⁺ T cells that results in normalization of their frequency in subjects who began treatment with higher baseline CD4⁺ T cell counts (>200 cells/μl).^{43,44} Subjects who began treatment with <200 CD4⁺ T cells/μl experienced partial restoration in CD4⁺ T cell numbers but not normalization of the naïve CD4⁺ T cell compartment, suggesting delayed initiation of cART may adversely affect immune reconstitution even in the absence of viral burden.⁴³

To develop an effective CTL-mediated immunotherapy that would allow the reduction or cessation of cART in chronically infected individuals, it is essential to evaluate the effects of untreated HIV-1 infection on the naïve CD8⁺ T cell compartment. Progressive HIV-1 infection is accompanied by decreases in the naïve CD8⁺ T cell subset despite increases in total CD8⁺ T cells.⁴⁵ Cossarizza et al. assessed CD4⁺ and CD8⁺ v-beta TCR repertoires in acutely and chronically infected subjects pre- and post-cART. Although the naïve CD4⁺ compartment was only restored in subjects receiving cART in acute infection, the naïve CD8⁺ compartment was restored with cART irrespective of when treatment began.⁴⁶ These findings suggest naïve CD8⁺ T cells in subjects on cART possess the breadth and specificity required to respond to an array of diverse HIV-1 antigens.

Perturbations in the normal distribution of TCRs within the naïve T cell repertoire of untreated HIV-1 infected persons have been noted.⁴⁷ These alterations lead to TCR clones being both more or less prevalent in HIV-1-infected subjects compared to healthy, uninfected age-matched donors.^{40,48} Baum et al. showed that while HIV-1-infected persons exhibited a tenfold decrease in TCR repertoire diversity in the blood, the diversity of purified T cell populations was comparable between HIV-1-infected and HIV-uninfected subjects.⁴⁹ They therefore postulate that changes in TCR repertoire diversity are the result of changes in T cell subpopulations and not the direct result of specific clonal deletion or expansion within the naïve compartment. These findings further underscore the potential efficacy of an immunotherapy aimed to stimulate primary anti-HIV-1 CTL responses from naïve CD8⁺ T cell precursors.

While changes in the frequency of naïve T cells may play a role in the generation of an effective immune response, their function in response to neo-antigen is of equal importance. Lange et al. evaluated antibody concentrations, lymphocyte proliferation, and delayed-type hypersensitivity responses following tetanus toxoid, diphtheria-toxoid, and key hole limpet hemocyanin immunization and showed that delayed initiation of cART predicted an impaired response to vaccination, despite partial restoration of CD4⁺ T cell numbers.⁵⁰ Gelinck et al. reported significantly lower concentrations of antirabies IgG and IgM following rabies vaccination in HIV-1 infected subjects compared to uninfected donors.⁵¹

While both of these studies demonstrated an impaired capacity to generate primary immune responses against neo-antigens, they also focused solely on Th2-driven antibody responses.

In an immunotherapy, however, the goal is to induce a CD8⁺ T cell-mediated response via potent HLA class I-restricted antigenic stimulation. Because of this, results from vaccines that aim to induce antibody-mediated immune responses in HIV-1-infected patients should be interpreted with caution when applying them to analyses of potential CTL-mediated immunotherapy efficacy. Additionally, these studies compare HIV-1-infected subjects on cART to uninfected donors, which is difficult when assessing naïve T cell function in response to primary stimulation without accounting for a variety of factors, including HLA type, individual differences in autologous APCs, age, comorbidities, duration of infection, etc. A more pertinent approach would be to confine the studies to the analysis of the individual HIV-1-infected subjects to determine if the proposed immunotherapy generates responses of efficacy greater than that generated through natural infection. Although the *de novo* response generated in an HIV-1-infected person on cART may not be equivalent to that which is generated in an uninfected person, it may be sufficient for viral clearance.

In the absence of immune dysfunction and during suppressive cART, it is plausible that an effective CD8⁺ T cell response could be generated from naïve precursors if induced by a potent antigenic stimulation, possibly in the form of an antigen-loaded DCs. These APCs may be able to overcome any deficiencies that exist in the naïve CD8⁺ T cell compartment and could provide the potent stimulus needed to induce an HIV-1-specific CTL response.

IV. TEACHING THE OLD DOGS NEW TRICKS

HIV-1-specific CTLs are effective at imposing immunological pressure in acute infection, as shown by their induction of a large turnover and mutation rate in the virus population.^{52–54} Their failure to control virus in chronic infection, however, is hypothesized to be due to several factors. Regulatory T cells have been shown to suppress HIV-1-specific T cell responses following DC immunotherapy in subjects on cART,⁵⁵ and have been implicated in HIV-1 pathogenesis and disease progression, the details of which have been reviewed elsewhere.^{56,57}

Prolonged antigenic stimulation in chronic HIV-1 infection also results in T cell exhaustion with concomitant upregulation of checkpoint markers, such as programmed cell death 1 (PD-1), CTLA-4, TIM3, and others.^{58–60} Programmed cell death 1 (PD-1) expression on HIV-1-specific T cells is associated with multiple parameters of T cell dysfunction, including impaired proliferative capacity and reduced cytokine secretion.^{61–64} Interestingly, PD-1 upregulation is not associated with CD8⁺ T cell exhaustion in long-term nonprogressors,⁶¹ suggesting a mechanism by which CTLs could initially control virus in typical HIV-1 progression but fail to do so in the chronic stages of infection, potentially due to the upregulation of immunological checkpoint markers. Because of these observations, PD-1 has been proposed as a target in HIV-1 immunotherapy.⁶⁵ Indeed, Youngblood et al. demonstrated an epigenetic program for PD-1 expression by CD8⁺ T cells following prolonged exposure to HIV-1,⁶⁶ suggesting immunotherapies targeting PD-1 may be of variable efficacy depending on the time of cART administration relative to infection.

To overcome this dysfunction in memory T cells, DCs could “recondition” or “reprogram” the endogenous memory T cells such that they effectively recognize and eliminate infected targets. Wesa et al. showed that type-1 polarized DCs can revitalize defective CD4⁺ T cell responses specific for melanoma-associated antigens.⁶⁷ Polarized DCs shifted the T cell response from one that predominantly secretes IL-5 to one predominantly secreting the type-1-associated cytokine, IFN- γ . Indeed, much of what we have learned regarding HIV-1 immunotherapy was pioneered in the cancer field, and perhaps memory T cell reconditioning could translate into HIV-1 immunotherapy as well. Recently, Deng et al. reported CTL elimination of CD4⁺ T cells infected with latent HIV-1 on peptide stimulation,⁶⁸ thereby suggesting that boosting the endogenous memory response is sufficient to induce targeting of the HIV-1 reservoir. While these findings support the function of recall HIV-1-specific CTLs, the longevity and efficacy of such a response in chronically infected patients on cART has yet to be evaluated. It is possible that prolonged antigenic stimulation throughout years of untreated infection generated a pool of memory CTLs with short-lived effector capacity. Despite this, reconditioning or “boosting” memory CD8⁺ T cells is an attractive approach, as memory T cells are much more frequent and have a higher percentage of antigen-specific cells that require less co-stimulation. In contrast, these cells also have a higher likelihood of possessing an exhausted phenotype, and while they may be specific for the immunotherapy antigen, they may also perpetuate an environment of exhaustion and immune dysfunction.

V. SHOULD WE LET THE SLEEPING DOGS LIE?

A more recent and less explored consideration is the effect of existing HIV-1-specific memory T cells on the efficacy of a DC immunotherapy that aims to induce primary CTL responses from naïve precursors. Despite their failure to control virus during treatment interruption, HIV-1-specific CD8⁺ T cells persist in the blood of subjects on ART. While only a small fraction of PBMC and purified CD8⁺ T cells from these subjects secrete IFN- γ in response to HIV-1 peptide antigens, DCs loaded with these same antigens reveal broad and robust T cell responses.^{22,33,69} Additionally, peptide-loaded DCs enhance the percent of T cells that secrete multiple type 1 cytokines, including IL-2, IFN- γ , TNF α , MIP1- β , and CD107a, and stimulate proliferation of T cells in response to MHC class I-restricted HIV-1 peptide epitopes.^{20,22,33} As the assays used in these studies range from 6 h to 18 h, it is highly unlikely that DCs are inducing primary responses, but are rather revealing T cell responses that were undetectable with standard assay procedures. These findings show that HIV-1-specific T cells persist during ART and are capable of secreting high levels of type 1 cytokines in response to HIV-1 antigens, yet are not effective at eliminating infected cells. These studies also suggest that these quiescent memory cells (aka “sleeping dogs”) can be awoken with the proper stimulus.

Of particular interest to us is the fact that the activity of highly avid HIV-1 antigen specific CTLs has been shown to be maintained throughout chronic stages of infection without any apparent impact on viral evolution.^{32,70–72} However, these responses can be shown to diminish once the subjects undergo cART, suggesting that these CTLs actively respond to autologous virus.⁸ Similarly, the successful establishment of CTL epitope variants arising during the acute stages of SIV infection has been shown to occur while in the presence of

preexisting variant reactive CTLs.⁷³ Related to these findings, in longitudinal studies designed to determine the impact of CTL responses on viral evolution and the frequency of epitope variants, our group also found evidence that antigen specific activity of CTL responders, naturally generated in the acute phase of HIV-1 infection against epitope sequences presented during early infection, can be maintained throughout infection against antigenic variants established at later time points.^{32,74} We found that these early arising CTL responders would secrete cytokines when challenged with autologous HIV-1 epitope variants that had evolved well beyond the time of T cell sampling. However, cytotoxicity mediated by these “cross-reactive” CTLs against autologous CD4⁺ T cell and immature DC targets was specific for the founder epitopes, while minimal killing was observed in those targets expressing the antigenic variants, suggesting that these CTLs may be “all bark and no bite.” This uncoupling of the T cell helper and killing functions, and the selective induction of the CTL cytokine production by the late-evolving variants, was found to create an inflammatory environment suitable for promoting DC maturation, chemotactic activity, and enhanced HIV-1 trans infection of CD4⁺ T cells, thus supporting the concept that we should let the sleeping dogs lie.

These findings have implications in the design of prophylactic and therapeutic vaccines and suggest that a form of “original antigen sin” may exist in the context of HIV-1. The presence of memory T cells specific for HIV-1 antigens may not only be ineffective at eliminating infected cells, but could potentially enhance viral spread on encountering a similar, yet different, antigen. Indeed, the STEP vaccine trial, which utilized an Ad5 vector containing the Gag, Pol, and Nef proteins, noted slight increases in the rate of HIV-1 infection among vaccine recipients.^{75,76} Despite this, T cell responses were detected in ~80% of vaccinated individuals.⁷⁷ Follow-up studies in vaccine recipients noted the expansion of CCR5-expressing, memory CD4⁺ T cells that were susceptible to HIV-1 infection.^{78,79} It is possible that among other compounding factors, memory T cells specific for the vaccine proteins actually enhanced infection when the patients encountered heterologous HIV-1. Although speculative in the context of HIV-1 vaccination, there is evidence of this in other disease models.⁸⁰

VI. CONCLUSIONS

While several studies have noted deficiencies in naïve T cells from HIV-1-infected persons on cART, this could be overcome by using potent APCs and appropriate antigenic stimuli. Perhaps the function of naïve T cells in these patients is less than those seen in HIV-negative persons, but maybe the response induced via a potent APC is still sufficient to eliminate infected cells. While HIV-1-specific memory T cells persist in subjects on ART, they are largely dysfunctional and may provide a barrier to successful CTL induction. A model outlining this hypothesis is shown in Fig. 1 and the immunological characteristics that favor targeting naïve T cells in a DC immunotherapy are described in Table 1. It may be of interest to develop methods of specifically targeting naïve T cells while minimizing memory T cell activation in immunotherapies. We therefore propose that an effective HIV-1 immunotherapy for persons on ART should teach the new dogs new tricks, but let the sleeping dogs lie.

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ABBREVIATIONS

APC	antigen-presenting cell
cART	combination antiretroviral therapy
CD	cluster of differentiation
CTL	cytotoxic T cell
DC	dendritic cell
HIV-1	human immunodeficiency virus type-1
IFN-g	interferon-gamma
IL	interleukin
PD-1	programmed cell death-1
TCR	T cell receptor

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FIG. 1.

Proposed outcome of DC immunotherapy targeting naïve and memory CD8⁺ T cells. DC priming of naïve CD8⁺ T cells will result in primary HIV-1-specific CTLs that are capable of producing multiple type-1 immune mediators and can effectively eliminate HIV-1-infected CD4⁺ T cells. We hypothesize that targeting memory CD8⁺ T cells in a DC immunotherapy will lead to cytokine production without elimination of latently infected CD4⁺ T cells and will perpetuate an environment of enhanced immune activation.

TABLE 1

Immunologic characteristics that favor targeting naïve T cells in a DC immunotherapy for HIV-1-infected subjects on cART

Characteristic	Findings	Refs.
Exhaustion/upregulation of coinhibitory molecules	PD-1 expression on CD8+ T cells is correlated with viral load, antigenic stimulation	62, 81, 82
	Differential epigenetic programming for PD-1 expression in memory compared to naïve CD8+ T cells	66, 83, 84
	PD-1 ^{hi} HIV-specific CTLs have impaired proliferative responses to antigen	62–64
	CTLA-4 expression correlates with viral load	85
	CD160-associated CD8+ T cell dysfunction	86
	CD160 expression is restricted to terminally differentiated and memory CD8+ T cells	87
	Tim-3 expression correlates with viral load, is associated with decreased cytokine production	88
T cell reactivity to early HIV-1 variants	CD8+ T cells derived from late infection or after cART continue to recognize early HIV variants	32, 33, 74
Regulatory T cells (Tregs)	Treg removal enhances recall HIV-specific T cell responses	55, 57, 89–92
	Treg expansion in chronic HIV infection	92
Selective programming via DC immunotherapy	Myeloid DCs of untreated HIV-infected persons express PD-L1, normalized after cART	93
	DCs can be engineered to prime a type-1 CTL response from naïve precursors	23, 31