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HIV-specific CD4 T cells and immune control of viral replication

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Abstract

Purpose of review—To understand the role of HIV-specific CD4 T cells in viral control and highlight recent progress in the field.

Recent findings—HIV-specific CD4 T cells show higher functional avidity in elite controllers than in subjects with progressive infection. There is an attrition of the HIV-specific CD4 T cell population in the digestive mucosa of ART-treated subjects that contrasts with robust responses in individuals with spontaneous viral control. Secretion of the cytokine IL-21, by HIV-specific CD4 T cells, is associated with disease control and enhances the capacity of HIV-specific CTL's to suppress viral replication. Studies of the PD-1, IL-10 and Tim-3 pathways provided insight into mechanisms of HIV-specific CD4 T cell exhaustion and new evidence that manipulation of these networks may restore immune functions. Robust, polyfunctional CD4 T cell responses can be elicited with novel HIV and SIV vaccines.

Summary—These observations show that HIV-specific CD4 T cell responses are different in elite controllers and individuals with progressive disease. Evidence suggests that HIV-specific CD4 T cells will be an important component of an effective HIV vaccine and significant efforts need to be done to further our understanding of HIV-specific CD4 T cell functions in different body compartments.

Keywords

HIV; CD4 T cell; elite controllers; IL-21; T cell exhaustion; mucosal immunity

Introduction

Since the initial descriptions of adaptive immune responses against HIV in infected individuals, research efforts in the HIV field have put a strong emphasis on CD8 T cell (CTL) responses with the goals of understanding the capacity of elite controllers (EC) to suppress viral replication and the development of a CTL-based vaccine. The recent outcomes of the STEP and the RV144 clinical trials[1–3**] highlighted the need for a rational vaccine design that will aim at inducing broader and stronger combined humoral and cell-mediated immune responses[4]. Numerous studies in animal models and data in humans provide strong evidence that CD4 help *in vivo* is critical for the generation of

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effective CTL and B cell responses[5] and for mobilizing CTLs to infected mucosa[6**]. Although the preferential infection of HIV-specific CD4 T cells raised the concern that this subset might fuel viral replication rather than contribute to its control[7], this relative increase is small and the large majority of HIV-specific CD4 T cells are not infected *in vivo*, even in the presence of high viral loads[7]. It is thus likely that vaccine-induced HIV-specific CD4 T cells will significantly contribute to effective immunotherapies against HIV.

Here, we review recent studies that examined differences in HIV-specific CD4 T cell responses between elite controllers and subjects with progressive infection. We also discuss data that shed light on mechanisms of CD4 T cell help and its functional impairment. Finally, we comment on virus–specific CD4 T cell responses generated by HIV vaccines.

Differences between in HIV-specific CD4 T cell responses of HIV controllers and individuals with progressive infection

Virus-specific CD4 T cell responses are impaired early in the course of HIV disease. The weak or absent HIV-specific proliferative CD4 T cell responses that are a hallmark of progressive HIV infection[8–10] were subsequently shown to be largely caused by loss of functions, in particular defective IL-2 secretion, and not physical deletion[11–13]. HIV-specific CD4 T cell responses are detectable in the large majority of HIV-infected individuals with current techniques (e.g. flow cytometry) but their magnitude is typically low and several fold smaller than the magnitude of CTL responses in the same subjects[11]. Studies showing that HIV-specific CD4 T cells in EC subjects maintained proliferative capacity *in vitro* compared to untreated individuals with progressive disease (CP) [14–16] suggested that these responses might have unique characteristics. Consistent with these findings, HIV-specific CD4 T cells of EC were shown to produce more IL-2 and to be more polyfunctional than those of CP subjects[11, 13, 17, 18], whereas the magnitude of HIV-specific CD4 T cell responses measured by IFN-γ secretion did not correlate with viremia[11]. Subsequent data comparing EC, CP and subjects with optimally controlled viral load on antiretroviral therapy (cART) demonstrated that the differences in proliferative capacity, IL-2 secretion and phenotypic markers observed were at least in part the consequence, and not the cause, of low viral load[17, 19–21].

Recent studies, however, showed that HIV-specific CD4 T cells in EC and CP individuals present differences that cannot be restored by antiviral therapy alone. Involvement of the gut-associated lymphoid tissue (GALT) is thought to be critical in HIV pathogenesis[22–25]. Ferre et al[26*] compared HIV Gag-specific CD4 T cell responses (measured by production of the cytokines IFN-γ, IL-2, TNF-α and MIP-1β) in peripheral blood and rectal mucosa from HIV controllers, CP and cART individuals. HIV-specific CD4 T cell responses were generally higher in the rectal mucosa than in peripheral blood. The total magnitude of mucosal HIV-specific CD4 T cell responses in controllers did not differ significantly from CP subjects, but was higher than in cART subjects. This is consistent with previous findings in PBMC showing a decrease in the number of virus-specific HIV-specific CD4 T cells after control of viral load by ART[27, 28]. This dependency of dysfunctional T cells on antigen persistence is consistent with various animal models[29]. The maintenance of virus–specific CD4 T cell responses in EC suggests a more functional, long-lived memory T cell population and/or a better capacity to respond to small antigen load. Additionally, the same study[26*] showed that controllers had higher frequency of mucosal HIV-specific polyfunctional CD4 T cells than CP and cART individuals. Further tissue studies are required to expand these data, as studies in animal models showed significant organ-specific differences in T cell responses[29].

Focusing on immunodominant HIV CD4 epitopes, Vingerts et al[30*] examined growth kinetics, Vβ repertoire, and avidity for antigen of HIV-specific CD4 T cell lines derived

from PBMC of EC, cART and CP subjects. They identified a subpopulation of HIV-specific CD4 T cells in EC endowed with a higher functional avidity compared to non-controllers. These differences were noted in responses specific for an HIV Gag p24 peptide previously shown to be immunodominant and presented by multiple HLA Class II alleles[31, 32]. Using HLA-Class II tetramers, the authors further demonstrated a higher functional of TCR binding avidity to the HLA-peptide complex in EC. This capacity of HIV-specific CD4 T cells in EC to respond to minimal amounts of antigen may contribute to higher magnitudes of HIV-specific CD4 T cell responses in EC compared to cART individuals[11, 17, 26].

Some previous studies suggested that HLA-DRB1*13 could be associated with immune control[33, 34]. Ferre *et al* [26*] found that controllers carrying the class II alleles HLA-DRB1*13 and/or HLA-DQB1*06 had the most robust HIV-specific CD4 T cell responses and that individuals that had both alleles showed highly polyfunctional mucosal CD4 T cells compared to those that had HLA-DQB1*06 alone or other class II alleles. However, the association of specific HLA Class II alleles with EC status remains to be confirmed in larger studies. While a recent large GWAS study[35**] confirmed the association of several HLA Class I alleles including B57 and B27 with viral control, no HLA Class II association reached genome–wide significance. Whereas mutations in epitopes targeted by CD4 T cells during early HIV infection have been described[36], no direct evidence of CD4 T cell-driven viral escape or HLA Class II footprint has been documented thus far. Clearly, further studies are required to better determine the link between specific HLA Class II molecules and characteristics of HIV-specific CD4 T cell responses.

Inhibitory receptors and HIV-specific CD4 T cell exhaustion

An important factor in the lack of pathogen clearance in chronic infection is T cell exhaustion, defined as the progressive loss of functions in antigen-specific T cells leading to ineffective T cell response[37]. T cell exhaustion is due both to progressive damage to the cellular machinery and to active suppression of functions[38], and is in part mediated by negative regulatory pathways that play an important role in maintaining peripheral tolerance and avoid excessive immune activation in physiologic conditions. T cell exhaustion is a gradual process, with some functions being lost early (proliferation, IL-2 secretion) while others, like IFN-γ secretion, are lost at an advanced stage of impairment[5], consistent with the characteristics of HIV-specific CD4 T cell responses at different disease stages.

Whereas several studies have investigated the role of Programmed Death-1 (PD-1), an inhibitory molecule of the B7:CD28 family, in HIV-specific CTL dysfunction[39], less is known on the role of immunoregulatory networks in HIV-specific CD4 T cell exhaustion[40]. P D-1 is upregulated on HIV-specific CD4 T cells[41, 42] and its expression level correlated with viremia[41]. Blockade of the PD-1 pathway with a PDL-1 blocking antibody increased HIV-specific CD4 T cell proliferation, with significant variability amongst the small cohorts of subjects investigated[41–43] . The observation that CTLA-4, another molecule of the B7:CD28 family, was also upregulated on HIV-specific CD4 T cells and mediated a reversible dysfunction of these responses[42, 44] demonstrated that multiple inhibitory receptors co-regulate virus-specific T cell impairment[40]. Kassu *et al*[45], recently extended these observations by examining expression of PD-1, CTLA-4 and another regulatory receptor, TIM-3, which has been shown to impair HIV-specific CTL responses[46]. Co-expression of all three receptors was more strongly correlated with viral load compared to the expression of each receptor individually. They also observed that in contrast to HIV-specific CTL, a high fraction of HIV-specific CD4 T cells that expressed inhibitory receptors also co-expressed CD28. PD-L1 blockade concurrent with CD28 stimulation had an additive effect in enhancing HIV-specific CD4 T cell proliferation *in vitro* compared to manipulation of either pathway alone, illustrating that concurrent

modulation of inhibitory and stimulatory receptors augmented restoration of HIV-specific CD4 T cell responses.

A recent study by Quigley *et al* investigated the transcriptional "signature" generated by PD-1 in HIV-specific CD8 T cells and found that this signature was highly enriched in progressors as compared to controllers[47*]. The authors used gene-set enrichment analyses that allowed them not only to compare transcriptional profiles between data obtained on primary CTLs and transfected model cell lines, but also to perform informative cross-species comparisons with the murine LCMV model[48]. The transcriptional factor BATF was found to be downstream of the PD-1 receptor and to b a key regulator of CTL exhaustion. The authors successfully used siRNA knockdown in primary HIV-specific T cells to demonstrate that silencing BATF expression not only restored IFN-γ secretion and proliferation by HIV-specific CD8 T cells but also augmented secretion of IL-2 by HIV-specific CD4 T cells, suggesting that BATF may play an important role in the dysregulation of CD4 T cells in HIV infection.

Taken together, these data suggest that as shown for virus-specific CTLs in the murine LCMV model[49*], HIV-specific CD4 T cells are controlled by complex layers of negative regulation resulting from the coexpression of multiple inhibitory receptors, and that the sets of inhibitory molecules controlling the CD4 and CD8 T cell responses are only partially overlapping. Whether manipulation of these immunoregulatory networks can be beneficial *in vivo* to complement ART or boost vaccine efficacy will require further studies. Careful monitoring of potential autoimmune side effects will be critical, as illustrated by the occurrence of an inflammatory colitis in a cancer patient treated in a recent trial with a blocking anti-PD-1 antibody [50].

Cytokines and HIV-specific CD4 T cell impairment: the roles of IL-10 and IL-21

Soluble factors, such as chemokines and cytokines, are both critical mediators of HIV-specific CD4 T cell functions and key regulators of this lymphocyte subset. Interleukin 10 (IL-10) has been shown to play a critical role in the balance between immunopathology and protective responses in infectious diseases[51, 52], and to facilitate the establishment of chronic infection in the murine LCMV model[53, 54]. In HIV infection, early studies[55, 56] have shown that plasma IL-10 levels increased with disease progression and that IL-10 blockade enhanced HIV Env-specific T cell proliferative responses in some subjects. Brockman *et al*[57*] further clarified the role of the IL-10 pathway in impairment of HIV-specific CD4 T cell responses. Antibody blockade of the IL-10 receptor (IL-10Rα) resulted not only in increased proliferation but also enhanced secretion of the cytokines IFN-γ and IL-2 by HIV-specific CD4 T cells. The effect of IL-10Rα blockade on proliferation correlated with IL-10 plasma levels and IL-10 RNA expression in PBMC. Investigating the source of IL-10, the authors showed that even though monocytes appeared to be the major source of IL-10, a variety of cell subsets contributed to the increased levels of IL-10 in HIV infection. Said *et al*[58**] showed a functional relationship between the IL-10 and PD-1 pathways, and established a link to microbial products whose translocation from the gut is thought to play an important role in HIV pathogenesis. The authors demonstrated that microbial products induce expression of PD-1 molecule on monocytes, and expression of PD-1 on these cells correlated with viral load. Triggering PD-1 signaling into monocytes induced IL-10 production. The inhibitory effect that PD-1 signaling into monocytes had on HIV-specific CD4 T cell proliferative responses was reversed upon IL-10R blockade, showing that the modulation of monocyte antigen-presenting functions by PD-1 is critically mediated by IL-10. This study demonstrates that besides inducing chronic immune activation in HIV infection[59], bacterial translocation through the damaged intestinal mucosa upregulates inhibitory pathways that impair virus-specific immune responses.

IL-21 is a γ-chain cytokines mainly produced by a subset of CD4 T cells, which are now termed T follicular Th cells (Tfh)[60]. IL-21 induces the development of Th17 cells, blocks the differentiation of regulatory T cells[61], maintains CD8 T cell function[62], regulates B cell differentiation[63, 64], and is important in regulating effector T cells in the gut[65]. Clinical trials with recombinant IL-21 are ongoing in cancer patients to boost immune responses[66], while excessive IL-21 production is thought to play a role in multiple autoimmune diseases[67].

Studies in the murine LCMV model showed that IL-21 produced by virus-specific CD4 T cells was critical in controlling chronic infection and in preventing exhaustion of CD8 T cells[68–70**]. In HIV infection, Iannello *et a*l observed decreased levels of plasma IL-21 in CP individuals, and found a positive correlation of plasma IL-21 levels with CD4 counts[71]. A subsequent study from the same group showed that only EC maintained normal plasma levels of IL-21 compared with HIV negative subjects. ART only partially restored production of this cytokine[72]. Stimulated bulk CD4 T cells from CP produced less IL-21 than CD4 T cells from EC. Recombinant human IL-21 prevented enhanced spontaneous apoptosis of CD4 T cells from HIV-infected subjects.

Yue *et al*[73] showed that in CP subjects, higher frequencies of IL-21 producing CD4 T cells correlated with lower viral load. However, control of viremia in EC and in ART-treated subjects was associated with low frequency of IL-21-secreting HIV-specific CD4 T cells. In contrast, Chevalier *et al*[74*], using a different technical approach, found higher levels of IL-21 secretion by HIV-specific CD4 T cells in EC than in cART individuals, with the lowest levels detected in CP subjects. Examining mechanisms of T cell help, the authors found that IL-21 increased perforin, granzyme A and B, and the degranulation marker CD107 in HIV-specific CTL and that addition of IL-21 increased the capacity of CTLs to inhibit viral replication *in vitro*[74]. These data suggest that HIV-specific IL-21+ CD4 T cells might contribute to the control of viral replication in humans and be important for an effective vaccine.

Virus-specific CD4 T cells and HIV vaccines

Studies performed in monkeys indicated the importance of cell-mediated immunity that could significantly reduce replication of simian immunodeficiency virus (SIV)[75–78]. Based on these data and because eliciting broadly neutralizing antibodies has proven to be a very challenging task, the first HIV vaccines were primarily designed to induce HIV-specific CTL responses since the prevailing view was that augmenting the CD4 T cells responses might lead to increased numbers of target cells available for infection[79].

The failure of the STEP trial[1, 2], based on a Ad5 adenoviral vector, was a major setback for the T cell-vaccine strategy. The CTL responses generated by this vaccine were weak and narrow[80]. One hypothesis proposed to explain the increased rate of HIV acquisition among vaccinees that had pre-vaccine anamnestic adenovirus-specific immune responses was the induction of vector-specific CD4 T cells that increased the number of target at mucosal sites[80]. However, recent studies suggest that this hypothesis might not be valid[81]. Major efforts are being dedicated to creating vectors that do not induce vector-specific immune responses[82, 83] and generate broader HIV-specific T cell responses, including CD4 T cell responses[84**].

The RV144 clinical trial, based on a poxvirus (canarypox/ALVAC) vector/recombinant gp120 combination, which showed a modest 31.2% efficacy in reducing HIV infection rates, has revived hope of an effective HIV vaccine[3**]. The correlates of immunity elicited by this vaccine are still not fully characterized. Even though the RV144 was designed to induce strong CTL responses, the only HIV-specific T cell responses found in vaccinees were weak

CD4 T cell proliferative responses[85] suggesting a potentially beneficial role of HIV-specific CD4 T in this trial. The RV144 study has strengthened the rationale for testing poxvirus-based vaccines and multiple candidate are now in clinical trials using different vectors and prime-boost regimens[86]. Poxvirus vectors are capable of inducing robust HIV-specific CD4 T cell responses in humans[87, 88] but there is currently no evidence that one type of vector is superior to the others to generate effective HIV-specific CD4 T cell responses.

Conclusion

The interest for the role of CD4 T cell responses in HIV infection has been reignited in recent years. Besides their critical role in orchestrating the different arms of the immune response, HIV-specific CD4 T cell responses may also have direct antiviral effector effects. A clarification of the role of HIV-specific CD4 T cells at mucosal sites should be of high priority in future studies. The latest data discussed here suggest that CD4 T cells play an important role in controlling HIV infection and highlight the need for a more vigorous investigation of the HIV-specific CD4 T cell responses in the perspective of developing an effective HIV vaccine.

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Keypoints

- HIV-specific CD4 T cells will likely be an important component of an effective HIV vaccine.
- An increasing number of qualitative differences in HIV-specific CD4 T cells between controllers and progressors are being identified, and some of these differences are not fully corrected by control of viral load on therapy.
- T cell exhaustion caused by chronic infection is governed by multiple inhibitory receptors whose expression patterns differ between HIV-specific CD4 and CD8 T cells.
- IL-21 secretion by HIV-specific CD4 T cells is decreased in progressive HIV infection, which may contribute to both B cell and CD8 T cell impairment
- It is likely that the renewed interest in HIV-specific CD4 T cells will lead in a near future to the development of reagents that generate more robust and effective HIV-specific CD4 T cell responses.