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Distinctive features of CD4 T cell dysfunction in chronic viral infections

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Abstract

Purpose of review—To describe recent advances in the understanding of virus-specific CD4 T cell dysfunction in chronic viral infections, with an emphasis on HIV disease. We highlight features that are distinctive for CD4 T cells, as opposed to their CD8 T cell counterparts.

Recent findings—CD4 T cell activation and differentiation are tightly controlled. Regulation of these processes depend on the context of initial encounter of the naïve CD4T cell with the cognate antigen and on ongoing external cues to the antigen-experienced CD4 T cell, in particular the inflammatory environment, which is prominent in HIV infection. Virus-specific CD4 T cell dysfunction results from a combination of an exhaustion program and skewing in Thelper lineage differentiation which impact function.. The CD4 and CD8 T cell exhaustion programs present similarities and distinct features. The sets of inhibitory co-receptors expression differs: while PD-1 and Tim-3 are upregulated on both HIV-specific CD4 and CD8 T cells, CTLA-4 is largely specific to CD4 T cells, whereas 2B4 and CD160 are biased toward CD8 T cells.

Summary—Understanding the molecular basis of HIV-specific CD4 T cell exhaustion and identifying key differences with CD8 T cell impairment will be critical to design effective therapeutic and preventive immunotherapies against HIV.

Keywords

HIV; CD4 T cell; T cell exhaustion; lineage differentiation; inhibitory co-receptors

Introduction

CD4 T cell responses play a critical role in the development of effective cellular and humoral antiviral immunity [1]. CD4 T cell depletion in murine models has firmly documented the crucial role of CD4 T cell help [2, 3] Furthermore, adoptive transfer of

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LCMV-specific CD4 T cells into mice with chronic LCMV infection restored the function of exhausted virus-specific CD8 T cells and reduced viral burden [4]. HIV infection is a prototypic example of the clinical relevance of CD4 T cells, setting the stage in understanding opportunistic infections and tumors associated with CD4 T cell loss. For example, a correlation was found between loss of CMV-specific CD4 T cell function and end-organ disease, and conversely, immune restoration and clinical improvement on ART [5]. During HCV infection, a robust early CD4 T cell response has been associated with subsequent viral clearance, whereas weak Thelper responses have been associated with subsequent development of chronic hepatitis C [6]. Multiple lines of evidence thus suggest that effective CD4 T cell responses will also be an important component of any effective therapeutic or prophylactic HIV vaccine. Although it is very difficult to discriminate causes and consequences of viral control for a specific immunological readout in humans in the absence of a specific intervention, studies in specific contexts have been informative in terms of characteristics of HIV-specific CD4 T cell impairment (e.g, investigation of elite controllers, who are subjects able to spontaneously control virus in the absence of therapy [7, 8], longitudinal studies from the time of acute infection and on/off ART, etc). The significant progress made over the past few years in understanding mechanisms of CD4 T cell dysfunction in chronic infections sheds light on pathways that may need to be targeted to improve CD4 T cell help against HIV. Here, we highlight important differences in exhaustion mechanisms between the CD4 and CD8 T cell compartments, a knowledge that will likely be instrumental in assessing desirable features of CD4 T cell responses elicited by therapeutic interventions to reach functional HIV cure or prevent infection.

Learning from mechanisms of CD8 T cell dysfunction

Naïve T cell activation and differentiation is a tightly orchestrated process that depends on the characteristics of the interaction with the antigen-presenting cell, the duration of antigen encounter, the strength of TCR signaling [9**] and the microenvironment. Alterations of these parameters can result in various states of T cell impairment, which include exhaustion (defined as a progressive loss of effector functions in the setting of antigen persistence), tolerance, anergy and senescence (reviewed in [10]). While distinction of these settings of impairment is useful and gives prominence to important differences in the differentiation programs of antigen-specific T cells [10, 11], it appears that these distinctions are also blurred by shared cores of gene expression changes, whose underlying epigenetic basis in the setting of viral infections is subject to active investigation [12]. It is particularly relevant for humans as a long-lived species with very diverse environmental exposure as compared to murine laboratory models, and whose CD4 and CD8 T cell repertoires appear to be shaped by previous exposures to persistent and non-persistent microorganisms, which in turn may impact on disease outcome [13**, 14]. While there are likely such interspecies differences, studies in the murine Lymphocytic Choriomeningitis (LCMV) model have been instrumental in the major progress made over the past several years in the understanding of mechanisms of T cell exhaustion in both animal models and humans (reviewed in [15]).

Studies in LCMV infection have led to identification of critical mediators of virus-specific CD8 T cell exhaustion, such as PD-1, and allowed critical proof-of principle studies of partial reversibility of antiviral functions by in vivo blockade (reviewed by V. Kuchroo et al

in this issue). Whereas initial work in infectious disease models lead the way, many of the mechanisms identified are shared with tumor-associated CD8 T cell exhaustion. It is actually in the oncology field that the major applications of these discoveries have been translated to clinical care thus far: blockade of the PD-1 pathway in several Phase III trials yielded remarkable results in diverse type of metastatic cancers [16–19]. The specific functions restored associated with positive outcome remain to be identified, and it is not clear whereas besides CD8+ tumor-infiltrating lymphocytes (TILs) other cells types, including CD4 T cells, play a critical role in tumor control. Advances have been slower in immunotherapy of chronic infectious diseases in humans, this being in due to better disease prognosis with current treatment regimens as compared to metastatic cancer (reviewed in [20]). During the exhaustion process, CD8 T cells appear to undergo a hierarchical loss of function that mirrors the accumulation of inhibitory co-receptors on the cell surface (Kuchroo et al in this issue, and [21]). Some of the critical transcriptional events determining these key features of the CD8 T cell exhaustion program have been discovered ([22–25]; reviewed by Kuchroo et al and Collins and Henderson in this issue). These advances also provide potential candidate genes, robust comparative benchmarks and validated experimental approaches for studies of virus-specific CD4 T cell dysfunction in chronic infection.

Skewed lineage differentiation contributes to CD4 T cell dysfunction in chronic viral infections

Compared to the CD8 T cells, less is known on the molecular determinants of virus-specific CD4 T cell dysfunction in chronic infections, including HIV. This slower progress reside in part in the overall lower frequencies of CD4 T cell responses compared to CD8 T cells in many infections, the breadth of the CD4 T cell repertoire, the shorter lifespan as HIV-specific CD4 T cells may be preferred targets of HIV compared to some other specificities [26], the reduced availability of some important tools (for example, MHC Class II tetramers are much more challenging to manufacture than their MHC Class I counterparts), and the indirect readouts of function - CD4 T cells act mostly by regulating functions of other immune cell subsets. A cardinal feature of CD4 T cells is their capacity to differentiate into functional subsets that express different sets of cytokines, co-signaling molecules and homing receptors, which ensure their ability to provide help to diverse immune cell populations in different body compartments [27]. Early work showing that cytokine production by CD4 T cells was not stochastic led to definition of CD4 T cell subsets as distinct lineages (TH1, TH2, and subsequently TH17, TFH, Tregs, etc). Whereas this conceptual framework was useful to identify molecular mechanisms that determine CD4 T cell differentiation, in particular “master transcription factors”, it imperfectly reflected *in vivo* dynamics of helper CD4 T cell responses in infections, autoimmune diseases and other pathological conditions. Newer data support of much more plastic behavior of CD4 T cell responses, which is in particular impacted by the inflammatory environment (a Th17 cell, for example can easily become an IFN- γ producer [28] CD4 T cells can change their profile of cytokine production and frequently acquired a “mixed” phenotype relative to classically defined lineages (reviewed in [29, 30]. There are many circumstances in which the expression of master regulators is transient or where cells express more than one master regulator. Their role has thus more to be understood as a network, rather than unique determinants [31–33]).

CD4 T cell plasticity also plays an important role in chronic viral infections and adds complexity to the understanding of Thelper impairment to persistent pathogens. It is important to note that some models of viral infection have shown both loss and gain of specific CD4 T cell functions. Like CD8 T cells, virus-specific CD4 T cells in chronic infection tend to become “antigen-addicted” and undergo attrition when not exposed to the pathogen. Also similar to CD8 T cells, LCMV-specific CD4 T cells in chronic LCMV clone 13 infection show decreased ability to proliferate and secrete IL-2 and TNF-, while production of IFN- γ is comparatively better preserved [34]. However, other functions such as IL-10 production [35, 36] and IL-21 secretion [37, 38] are increased as compared to infection with the acute LCMV Armstrong strain. IL-21 is an important cytokine for both CD8 T cells and B cells and data suggest that at least part of the Tfh-mediated help for humoral responses is maintained. It is important to note that in the absence of CD4 depletion, LCMV Clone 13, which frequently used as a prototypic chronic infection model in mice, is ultimately controlled in the periphery after 60 to 80 days [2, 3]. In this setting,, helper T cell development are geared by chronic antigen stimulation away from Th1 polarization towards a T follicular helper-like phenotype, which contribute to the delayed viral control [39]. This illustrates the potential advantages of CD4 T cell plasticity in redirecting development toward a lineage beneficial to the host. LCMV Clone 13 infection mimicks in some aspects the dynamics observed in human HIV controllers and HCV resolvers in whom control of viral replication is frequently only achieved several weeks after acute infection. The fact that HIV-specific CD4 T cells from elite controllers are able to produce significantly more IL-21 than those of progressors [40] can be relevant in this regard. How dependent-and thus potentially reversible – is CD4 T cell lineage skewing dependent on external cues, including repetitive TCR stimulation and the inflammatory environment? Adoptive transfer experiments suggest that CD4 T cell might be more plastic than their CD8 T cell counterparts [41].

These findings are at least in part mirrored in major chronic viral infections in humans. CD4 T cell proliferative capacity to HIV [42] and HCV [43] is lost in chronic infection, and associated by reduced “polyfunctionality”, i.e the capacity of individual cells to produce multiple cytokines, in particular a reduced ability to produce IL-2 [44–46]. In contrast to CD8 T cells [47], control of viral load by antiviral therapy (ART) significantly restores proliferation and IL-2 secretion by HIV-specific CD4 T cells [48], suggesting that at least part of the differences in HIV-specific CD4 T cell features noted between elite controllers and progressors is a consequence, rather than a cause, of viral control. Data in HIV and HCV infections also suggest some skewing of lineage differentiation consistent with animal models. These viruses frequently elicit large quantities of CD4 T cell-dependent virus-specific antibodies that in some cases can even cause immunopathology (e.g, HCV-related vasculitis due to deposition of immune complexes [49]). Changes in the Tfh compartment in lymphoid tissues of HIV-infected individuals include a quantitative expansion and qualitative defects that do not preclude development of broadly neutralizing antibodies in individuals with high viral loads ([50a**, 50b**, 51*, 52] reviewed in detail by Cubas et al in this issue). Taken together, these data suggest that plasticity of CD4 T cell responses play a major role in chronic viral infections, including HIV, and that skewing of Thelper properties may have either positive or detrimental effects depending on the context.

CD4 T cell exhaustion as a distinct cell fate program

The alterations of CD4 T helper cells that include not only mere loss of functions but – at least in some infectious disease contexts - skewing toward new/mixed lineage subset properties raise the question as to whether CD4 T cells are also subjected to a real cell-intrinsic exhaustion program. Studies initiated in HIV infection have been quite informative in this regard, and support the concept of CD4 T cell exhaustion. Shortly after that the role of the PD-1 pathway was demonstrated for HIV-specific CD8 T cells, its implication in HIV-specific CD4 T cell impairment was demonstrated in *in vitro* experiments. The PD-1 molecule is upregulated on virus-specific CD4 T cells [53–55] and its expression was correlated with markers of HIV disease progression, positively with viral load and negatively with CD4 count. Blockade of the PD-1 pathway *in vitro* using blocking antibodies restored proliferation and cytokine secretion by HIV-specific CD4 T cells [53–56]. PD-1 expression appears to vary according to anatomic sites, with higher levels observed in lymph nodes compared to peripheral blood [54]. Although ART reduces PD-1 expression levels on HIV-specific T cells, it does not abrogate it completely. Consistent with this observation, blockade of the PD-1 pathway was found to be effective at restoring CD4 T cell cytokine production *in vitro* in ART-treated subjects, although to a lesser extent than in subjects with ongoing viral replication [55]. Such observations are made possible by the development of finer *in vitro* assays to assess the impact that different mediators of dysfunction have on the cytokine secretion profile of Thelper cells [57]. These results suggest a potential role of immunotherapeutic interventions targeting this pathway as an adjuvant to ART. More recently, PD-1 was shown to regulate function of Tfh cells and blockade of the PD-1 pathway restored HIV-specific Tfh help to B cells resulting in enhanced HIV-specific immunoglobulin production *in vitro* [50].

Besides PD-1, other inhibitory co-receptors have been identified as contributing to HIV-specific CD4 T cell impairment. Another member of the B7:CD28 family, CTLA-4, was also shown to play a critical role in CD4 T cell dysfunction. Similar to PD-1, CTLA-4 is upregulated on HIV-specific CD4 T cells and mediated a reversible T cell dysfunction [53, 58]. However, in contrast to PD-1 that regulates both CD4 and CD8 T cell responses, CTLA-4 overexpression and functional impact are largely specific restricted to HIV-specific CD4 T cells. Further studies demonstrated that co-expression of PD-1, CTLA-4 and another co-inhibitory receptor, TIM-3, was associated with a more exhausted HIV-specific CD4 T cell phenotype [59]. These findings are further supported by a recent study in the LCMV mouse model which demonstrated that the percentage of virus-specific CD4+ T cells decreased as the number of co-expressed inhibitory ligands increased [60]. Further investigations confirmed major differences in the sets of inhibitory co-receptors modulating HIV-specific CD4 and CD8 T cell responses (summarized in Figure 1): in contrast to HIV-specific CD8 T cells, CD4 T responses do not express significant levels of the inhibitory molecules CD244 (2B4) and CD160 [55]. Blockade of co-inhibitory receptors on HIV-specific CD4 T cells can have robust additive effects with blockade of cell-extrinsic pathways associated with CD4 T cell impairment. One such pathway is IL-10, which has been shown in several studies to be upregulated in HIV infection and able to inhibit CD4 T cell function [61, 62]. When compared to PD-1 blockade, IL-10 blockade appear to preferentially restored IFN- γ secretion as compared to other cytokines, consistent with its

known role as inhibitor of Th1 responses. Combining PD-1 and IL-10 blockade *in vitro* has a strong additive impact on some HIV-specific CD4 T cell functions, like IFN- γ but not others, like IL-13 production [63*]. This suggests that immune interventions targeting different mechanisms may differentially restore specific CD4 T cell functions. It is interesting to note that while investigations in SIV-infected non-primate primates is a critical step before interventions in humans, recent work in humanized mice have shown promising results for a small animal model of immunotherapeutic intervention in HIV infection: two studies in such systems led to reduction of HIV viral load and increase in CD4 T cell counts upon PD-1 blockade [64*, 65*].

In a recent study based on the murine LCMV model, the authors performed a genome-wide transcriptional analysis of virus-specific CD4 T cell and CD8 T cells in acute and chronic infections that yields important information on the molecular basis of CD4 T cell dysfunction in chronic viral infection [66**]. The data suggest the presence of shared mechanisms of CD4 and CD8 T cell exhaustion, as well as establish unique features of a CD4 T cell exhaustion signature that demonstrate that these subsets differ in some key features. Features identified include expression of different patterns of co-inhibitory and co-stimulatory molecules (consistent with the findings in HIV infection), cell cycle changes and DNA repair molecules, IFN type I signaling and a unique profile of transcription factors in exhausted CD4 T cells. Compared to acute resolving infection, there was a loss of a strong Th1-associated signature in chronic disease without obvious skewing toward canonical T helper lineages, although several Tfh-associated genes were upregulated. This study thus provides a reference framework to investigate further mechanisms of CD4 T cell exhaustion and interventions to restore functions.

Conclusion - CD4 T cell dysfunction: not a copycat of CD8 T cell impairment

Whereas CD8 T dysfunction in chronic viral diseases is strongly linked to a distinct exhaustion program, alterations of pathogen-specific CD4 T cell functions result from a broader combination of skewed lineage differentiation and of an exhaustion program characterized by features common to the two T cell subsets and by factors unique to T helper cells. These two categories of mechanisms are present in HIV infection, along with CD4 T depletion in the case of progressive disease. Furthermore, recent work in different pathogenesis models, in particular in autoimmune diseases, have exemplified a previously unappreciated degree of functional plasticity of CD4 T cells in inflammatory environments, which can have significant implications for HIV infection. Therefore, interventions to elicit or restore effective HIV-specific CD4 T cells need to be tailored to the specificities of this immune cell subset and may differ from those focusing on CD8 T cells. Further investigations are needed to investigate underlying mechanisms of CD4 T cell dysfunction in chronic viral infections in humans, which may differ significantly depending on the offending pathogen.

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Key points

- CD4 T cell play a key role in effective antiviral immune responses
- Mechanisms of CD4 T cell and CD8 T cell impairment differ in key aspects
- Recent studies of Thelper cells have revealed more functional flexibility in cytokine production than predicted by earlier work, and this plasticity plays an important role in different pathogenesis models.
- Virus-specific CD4 T cell dysfunction results from combination of an exhaustion program and skewing in Thelper lineage differentiation which impact function
- HIV-specific CD4 T cell function can be restored by manipulation of inhibitory molecules that mediate exhaustion, such as PD-1
- Whether immunotherapeutic strategies targeting CD4 T cell defects can complement ART to help achieve functional HIV cure needs to be determined

Figure 1. HIV-specific CD4 and CD8 T cells are governed by different sets of inhibitory receptors

Whereas some molecules have similar overall range of expression on both subsets (PD-1, Tim-3), CTLA-4 is preferentially expressed on CD4 T cells, CD244 and CD160 on CD8 T cells.