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Pathogen-specific T cell depletion and reactivation of opportunistic pathogens in HIV infection

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Abstract

During HIV infection, it is unclear why different opportunistic pathogens cause disease at different CD4 T cell count thresholds. Early work showed that CD4 T cell depletion is influenced both by cellular activation status and expression of viral entry receptors. More recently, functional characteristics of the CD4 T cells, such as cytokine and chemokine production, have also been shown to influence cellular susceptibility to HIV. Here we examine how functional differences in pathogen-specific CD4 T cells could lead to their differential loss during HIV infection. This may have implications for when different opportunistic infections occur, and a better understanding of the mechanisms for functional imprinting of antigen-specific T cells may lead to improvements in design of vaccines against HIV and opportunistic pathogens.

HIV-induced CD4 T cell depletion increases susceptibility to opportunistic pathogens

Untreated Human Immunodeficiency Virus-1 (HIV) infection leads to Acquired Immunodeficiency Syndrome (AIDS), a disease characterized by immune suppression and a loss of immune-mediated control against diverse opportunistic pathogens. Immune suppression in AIDS results from the progressive loss of CD4 T cells brought on by persistent HIV replication. While the pathogenic mechanisms underlying CD4 T cell loss by HIV have been widely debated, a simple rule still applies: the lower the number of CD4 T cells, the higher the risk of opportunistic infections. However, the timing of opportunistic infection is not strictly related to the extent of CD4 depletion for a given pathogen. Some opportunistic pathogens, such as Mycobacterium tuberculosis, can reactivate at relatively high CD4 T cell counts, whereas other pathogens, such as cytomegalovirus (CMV) or toxoplasma gondii, typically reactivate and cause disease only after CD4 T cells have dropped substantially (eg <100/μl).

Whether the difference in the timing of infection between opportunistic pathogens relates to the requirements for total CD4 cell numbers to control a given pathogen, or if it is due to

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differences in the number and/or quality of opportunistic pathogen-specific CD4 T cells at different stages of total CD4 T cell depletion is unclear. However, arguing for the latter, CMV end-organ disease in AIDS patients closely correlates with depletion of CMV-specific CD4 T cell responses [1–3]. Initiation of antiretroviral therapy (ARV) stops HIV replication, restores both total and opportunistic pathogen-specific CD4 T cells and leads to clearance or control of opportunistic infections [4]. Thus, depletion and functional defects of pathogen-specific CD4 T cells most probably contribute to the co-pathogenesis of HIV and particular opportunistic infections. Here we examine recent data suggesting that HIV infection and depletion rates of pathogen-specific CD4 T cells might differ depending on the cellular maturation or functional status, at least for Mycobacterium tuberculosis (MTB)-specific and CMV-specific CD4 T cells [5–6]. These findings might provide insight into why certain opportunistic infections occur or reactivate at different total CD4 T cell counts.

Viral entry receptors and CD4 T cell depletion

HIV entry into T cells is dependent on expression of the primary HIV receptor CD4 and one of two chemokine receptors: CCR5 or CXCR4 [7–8]. HIV transmission occurs almost exclusively with CCR5-tropic HIV strains [9]. Historically, CCR5-tropic strains have been referred to as “M-tropic”, because of their potential to infect both macrophages and primary T cells. CXCR4-tropic strains typically appear late during the course of HIV disease progression, are more cytopathic and have historically been referred to as T-tropic because of their ability to infect transformed T cell lines [10]. CCR5 expression is common on memory CD4 T cells in mucosal lymphoid tissues, the mucosa of the reproductive tract and intestine, the lung, and inflamed tissues [11–13] and cells in these locations are frequent targets for HIV infection. CXCR4 is expressed on naïve CD4 T cells, a minor fraction of peripheral memory CD4 T cells [14] and on CD4 T follicular helper cells that reside in central lymphoid structures [15]. Antigen-specific stimulation induces CCR5, but reduces CXCR4 expression by memory CD4 T cells in vitro [16–19]. Thus antigen-specific stimulation would promote HIV infection of responding CD4 T cells via CCR5 during their subsequent expansion and differentiation in vivo [6, 16]. This is supported by the relatively high cell-associated viral load of circulating transitional CD4 T cells ($CD28^+$ and $CCR7^-$), which are on the pathway to full CD4 T cell differentiation [20].

After transmission of CCR5-tropic HIV there is a rapid and profound depletion of $CCR5^+$ memory CD4 T cells from mucosal effector sites [12, 21]. This early decline in memory CD4 T cells is thought to occur due to cell death resulting from: 1) direct infection; 2) bystander effects from infected CD4 T cells; and 3) downstream immune activation [22–24]. Depletion of antigen-presenting cells, in particular dendritic cells (DCs), might also contribute to dysfunction or depletion of pathogen-specific T cell responses in HIV-infected subjects [25–27]. The expression of CCR5 on activated and dividing CD4 T cells certainly contributes to the early selection of CCR5-tropic strains [28–29] and to the depletion of pathogen-specific CD4 T cells during early and chronic HIV infection.

Integrin α4β7 in transmission and early dissemination of HIV

High integrin α4β7 expression defines a subset of memory CD4 T cells within genital mucosa, the rectum and the gut associated lymphoid tissue (GALT). The integrin α4β7 was recently described as a cellular receptor for HIV on CD4 T cells [30–31]. It contributes to efficient entry of HIV into the cell by capturing virions in close spatial proximity to the viral entry receptors CD4 and CCR5 [32–33]. Many cells in this population also express the viral coreceptor CCR5 and are in the active phase of the cell cycle, as defined by expression of Ki67 [33]. In vitro, $\alpha4\beta7^{high}$ CD4 T cells are highly susceptible to HIV infection and therefore represent an ideal substrate for viral replication [33]. Whether the amount of α4β7

expressed contributes to the infection or depletion rate of pathogen-specific CD4 T cells has not been studied specifically, but preferential depletion of circulating gut-homing CD4 T cell subsets during acute HIV infection suggest that this might be the case [34]. The discovery of this additional cellular receptor may provide a further link between sexual transmission, early virus dissemination and the early depletion of memory CD4 T cells in the GALT.

T cell activation status and HIV infection

T cell activation and proliferation contribute to productive HIV infection of memory CD4 T cells [35–38]. Expression of HLA-DR and CD25 (IL-2 receptor alpha chain) on CD4 T cells within lymphoid tissue explants defines the main target CD4 T cell population for productive HIV infection [35]. Indeed, the IL-2 signalling pathway, which is essential for clonal expansion after antigen-specific T cell stimulation, promotes HIV replication [6, 36]. Other cytokines that promote T cell turnover, in particular IL-15, also increase viral replication [39–40]. Thus a substantial fraction of antigen-specific CD4 T cells might die as a result of either complete or abortive infection by HIV, thereby reducing the generation and maturation of pathogen-specific memory CD4 T cells. Abortive HIV infection of CD4 T cells is characterized by incomplete reverse transcription of the viral genome and leads to cell apoptosis through the induction of cellular host defence mechanisms [41]. Potentially, such a mechanism further enhances death of newly generated pathogen-specific CD4 T cells. This hypothesis is supported by the dramatic loss of short-lived effector memory CD4 T cells within effector sites, such as the lung, during experimental SIVmac239 infection. These cells have a high rate of turnover in lymphoid tissues in the absence of SIV infection, a characteristic that presumably contributes to their infection and depletion by SIV prior to their arrival at effector sites [11, 42]. Hence, cytokine signalling pathways and the downstream cellular events associated with activation and proliferation of antigen-specific memory CD4 T cells also promote productive HIV or SIV infection. Extensive cellular depletion is then thought to occur at two stages: first, during the initial stimulation and early expansion phase from naïve or memory T cell pools, and second during the phase of homeostatic maintenance of antigen-specific memory T cells.

CD4 T cell specificity and HIV-induced depletion

Both MTB and CMV typically cause latent or controlled infection in immunocompetent individuals but can reactivate and cause disease during periods of immunosuppression, and both infections appear to be controlled predominantly by pathogen-specific CD4 T cells [1, 3, 43–44]. Despite these similarities, the CD4 T cell thresholds at which these infections cause opportunistic disease are very different: active TB disease is often the first severe opportunistic infection affecting HIV^+ patients in MTB endemic areas [45–46], whereas CMV end-organ disease typically occurs only after CD4 counts have declined to very low numbers. MTB-specific CD4 T cell responses are depleted relatively early after HIV infection (<12 months) and are significantly reduced in peripheral blood and bronchalveolar lavage during chronic HIV infection [6, 47–48] in subjects with latent infection. In contrast, CMV-specific CD4 T cells persist until late stage HIV infection [5–6, 49] but their eventual loss still precedes CMV end-organ disease [1–3]. These results imply that MTB-specific CD4 T cells are particularly vulnerable to HIV infection and depletion. Likewise, HIV reduces Streptococcus pneumonia-specific CD4 TH1 cell responses and invasive pneumococcal disease is often observed in HIV patients with relatively preserved T cell numbers[50]. The differential depletion of pathogen-specific CD4 T cells provides a potential explanation for the different CD4 T cell thresholds for active opportunistic disease caused by these pathogens during HIV infection.

Phenotypic differences might contribute to the early depletion of MTB-specific CD4 T cells and persistence of CMV-specific CD4 T cells. Most studies of immunodeficiency virus infection and depletion of CD4 T cells have stratified T cell subsets using markers of cellular activation and maturation such as CD45RO/RA, CD62L, HLA-DR, Ki67 or CCR5. Parameters associated with HIV-induced depletion of CD4 T cells of defined specificity are less clear. MTB- and CMV-specific CD4 T cells populations express similar amounts of CCR5[6]. However, during latency, most MTB-specific CD4 T cells are $CD27^{+}CD57^{-}$, which together with the frequent expression of CCR5 on these cells, is consistent with a transitional or early differentiated phenotype [47]. In contrast, CMV-specific CD4 T cells are almost exclusively $CD27^{-}$ and typically contain a large proportion of $CD57^{+}$ cells consistent with an effector memory and terminally differentiated (more mature) phenotype. CD4 T cells that express CD57 have a reduced capacity to proliferate and a lower cellular HIV load in vivo [5, 51]. Thus as antigen-specific CD4 T cells become more differentiated (probably as a result of more vigorous antigenic stimulation by opportunistic pathogens) they tend to express more CD57, are less able to proliferate, and are less likely to become infected by HIV.

There are also functional differences in MTB- and CMV-specific CD4 T cells that could impact susceptibility to HIV infectivity. For example, it is well known that CCR5 ligands can protect CD4 T cells from infection with CCR5-tropic HIV strains in vitro, probably by blocking the interaction of HIV envelope protein gp120 with CCR5, which is necessary for viral entry into the target cell [52]. The CCR5 ligand MIP-1β is highly expressed in CMV-specific CD4 T cell populations, whereas during latency most MTB-specific cells do not produce MIP-1β [6]. Recent data suggest that autocrine production of the CCR5 ligand MIP-1β by CMV-specific CD4 T cells is operative in protecting these cells from infection in vivo [5]. The state of T cell maturation may determine the capacity of a cell to produce MIP-1β; terminally differentiated $CD57^{+}$ CMV-specific CD4 T cell typically secrete MIP-1β upon restimulation (figure 1) [5-6]. These results link T cell maturation, the production of CCR5 ligands and cellular resistance to HIV infection, and support the hypothesis that autocrine production of CCR5 ligands and a reduction in proliferative potential can render certain antigen-specific CD4 T cells moderately resistant to HIV infection. IL-2 production also differs between these pathogen-specific T cells: IL-2 is produced by the majority of MTB-specific CD4 T cells but only a small minority CMV-specific CD4 T cells. IL-2 supports proliferation of CD4 T cells and might promote HIV infection of MTB-specific CD4 T cells [6].

Of note, during latent TB infection MTB- and HIV-specific CD4 T cells share several functional and phenotypic characteristics (Figure 1); a majority of cells are $CD27^{+}$ and produce little or no MIP-1β. Furthermore, when compared to CMV-specific or the total memory population, HIV- and MTB-specific CD4 T cells are preferentially depleted and carry similar levels of HIV gag DNA. These results are consistent with the hypothesis that infection and depletion of different pathogen-specific CD4 T cell populations are influenced by their functional and phenotypic characteristics [5-6, 53], with potential implications for HIV vaccine design (text box 1).

Box 1

How functional and phenotypic analysis of vaccine induced CD4 T cells could support optimization of HIV vaccines

Phenotype and function of vaccine-induced T cells can be modulated through use of different vaccine vectors and thus can potentially be optimized to induce HIV-specific CD4 T cells that are partially resistant to HIV infection. Preferential HIV infection of vaccine induced CD4 T cells is a major concern for HIV vaccine developers, because

such a mechanism would lead to rapid depletion of vaccine-induced immunity upon encounter with HIV. In this context, vaccine-mediated induction of HIV- and vector-specific CD4 T cells of a mature phenotype with a high capacity to secrete CCR5 ligands, such as MIP-1β, could potentially protect these cells from being infected with HIV. SIV vaccine vectors based on replication competent CMV induce highly protective effector memory T cell responses that are associated with SIV-specific CD4 T cells with a high capacity to secrete MIP-1β upon stimulation [92]. In contrast, responses induced by BCG vectors could produce antigen-specific CD4 T cells that are highly susceptible to infection and depletion by HIV.

Antigen stimulation history affects CD4 T cell phenotype and function

Antigen exposure can influence CD4 T cell phenotype and function, and thus potentially affects susceptibility to HIV. In situations in which antigen is cleared, for example after tetanus toxoid vaccination, the antigen-specific CD4 T cells predominantly express a less differentiated, central memory phenotype, and produce IL-2 upon restimulation. Infections with low, but persistent antigen levels, such as latent/recurrent CMV or non-progressing HIV infections, are associated with more differentiated pathogen-specific CD4 T cells that produce less IL-2 [54-55]. Frequent reactivation of opportunistic infections also potentially contributes to the depletion of pathogen-specific CD4 T cell via the mechanism of T cell exhaustion. Latent MTB infection probably falls somewhere between true clearance (as seen for tetanus toxoid vaccination) and the more persistent antigen expression that is observed in CMV and HIV infections. Overall, different conditions of antigen exposure and persistence affect phenotypic and functional characteristics of pathogen-specific CD4 T cells [54]. Consistent with this is the observation that the higher antigen load in active, as compared to latent, tuberculosis drives maturation of MTB-specific CD4 T cells towards a more mature, $CD27^{-}$ phenotype [56–57], and these cells have an increased capacity to secrete MIP-1β and a decreased capacity to produce IL-2 [6]. Indeed, MTB-specific CD4 T cell responses can be detected in some HIV patients even with low CD4 T cell count in HIV+ subjects and are often associated with active symptomatic or subclinical, yet active TB [6, 58–61]. Thus, changes in the function and phenotype of MTB-specific and other pathogen-specific CD4 T cells during disease and changes in antigen load, potentially alters their susceptibility to HIV infection [6, 56, 60, 62]. Putative cellular parameters that are associated with an increased or decreased susceptibility to HIV infection of antigen-specific CD4 T cells are summarized in table 1.

Antigen-presenting cells (APC) contribute to HIV infection of CD4 T cells

Conjugates of APCs (including DCs) and T cells are the predominant sites for HIV replication in vivo [63]. Infected DCs preferentially transmit HIV to responding antigen-specific CD4 T cells [64], a process that would contribute to efficient infection and subsequent depletion of newly emerging antigen-specific CD4 T cell populations during the expansion phase [53]. Not only are DCs crucial for the transfer of HIV to responding CD4 T cells, the co-stimulatory molecules and cytokines/chemokines they express can influence the function and phenotype of the responding CD4 T cells, which may further influence susceptibility to infection and subsequent HIV replication [65]. For example, DC production of proinflammatory cytokines (eg TNF) and stimulation of T cell surface molecules such as CD40 and B7-family members induce HIV replication and promote infection of T cells that interact with DCs [66]. Recognition of microbial products through pattern recognition receptors, such as the Toll-like receptors, modulate DC costimulatory properties during T cell priming [67]. Hence, innate microbial stimuli probably play a central role in the type of CD4 T cell response that is generated against various pathogens, and might therefore

influence the likelihood that an antigen-specific CD4 T cell will become infected and depleted by HIV.

Depletion of CD4 T helper (Th) 17 cells contributes to impaired mucosal barrier function of the gut

Profound depletion of GALT memory CD4 T cells during HIV infection [12, 68] results in impaired mucosal immunity and systemic immune activation, which are hallmarks of pathogenic immunodeficiency virus infection [27]. Memory Th17 cells are found in high frequency in GALT [69] and their depletion plays a central role in the translocation of microbes and their products into the blood stream promoting systemic immune activation [27, 70]. The extent of immune activation is an important predictor of subsequent HIV disease progression [71]. The selective loss of mucosal Th17 cells may thus be important in the general pathogenesis of HIV.

In humans, Th17 cells appear to specifically target extracellular bacterial and fungal pathogens promoting their clearance [27, 72–73]. Thus Th17 cell depletion probably sets the stage for increased susceptibility to many opportunistic bacterial and fungal infections and certainly contributes to systemic dissemination of enteric infections in HIV patients [74]. Susceptibility of Th17 cells to HIV-infection is similar to that of Th1 cells. This probably relates to the fact that Th17 cells are highly activated cells in the gut which are under continuous exposure to bacterial antigens, and this promotes direct infection by HIV [69].

Depletion of pathogen-specific CD4 T cells might promote development of virus- associated malignancies in HIV infection

Loss of control of some viral pathogens can lead to cancer rather than disseminated infection. Cancers and lymphoproliferative disorders occurring in patients with HIV infection are often closely linked to oncogenic viruses, such as the gamma Herpes viruses Epstein-bar (EBV) and Kaposi Sarcoma Virus (KSV), or Human Papilloma Virus [75–78]. Perhaps most thoroughly studied are malignancies associated with HIV-induced immunosuppression that are caused by EBV co-infection**,** which typically occur only after CD4 T cell counts have dropped substantially. Development of EBV-related lymphomas in HIV-infected patients is associated with a loss of EBV-specific T cell function. In particular, EBV-specific CD4 T cells targeting the latency associated Epstein-Barr virus nuclear antigen (EBNA) 1 are preferentially lost in patients who progress to AIDS-related non-Hodgkin lymphoma [79]. Similarly, HIV+ patients that develop primary lymphoma of the central nervous system lack EBV-specific CD4 T cell responses [80], suggesting a role for the depletion of EBV-specific CD4 T cells in malignant B cell transformation by EBV. The mechanism for this cellular depletion is not known, but it has been hypothesized that EBNA1-specific CD4 T cell responses might be driven by proliferating EBV-infected B cells within secondary lymphoid organs. These areas support extensive HIV replication, which could potentially contribute to infection and depletion of EBNA1-specific CD4 T cells [79, 81-82]. Alternatively, frequent reactivation of EBV in HIV+ subjects [83] might drive cellular maturation of these cells, associated with an increased capacity for Mip-1β secretion, which is associated with partial resistance to HIV infection. Depletion might then be mediated through exhaustion rather than by direct infection of these cells.

HIV infection also significantly increases the incidence of Human Papilloma Virus (HPV) associated cervical cancer and other anogenital malignancies, even in the era of highly active antiretroviral treatment [75–76]. HPV infection in HIV^+ subjects is characterized by a higher prevalence of persisting infections caused by multiple HPV types, more rapid disease

progression (mean of 3 years vs. 15 years in HIV^- subjects) and less frequent spontaneous regression [84–85]. Many HPV-associated lesions and cancers in HIV^+ subjects are associated with non-16/18 HPV types, and would therefore not have been preventable by existing vaccines [86–87]. While vaccine-induced protection against HPV infection is mediated by antibodies, other evidence suggests that, once infection is established, T cells are responsible for controlling malignant outgrowth. Specifically, spontaneous regression of HPV-associated warts occurs in the presence of infiltrating memory CD4 and CD8 T cells [88] while a lack of HPV-specific CD4 T cell responses predisposes to HPV-associated cervical cancer [89–91]. While little is known about the influence of HIV infection and ARVs on the frequency and characteristics of the CD4 T cell response to HPV infection, the increase of HPV-associated cancers in HIV^+ humans implies that defects in the HPV-specific CD4 T cell response play an important role.

Concluding remarks

Not all pathogen-specific CD4 T cells are created equal and this may have implications for opportunistic infection during HIV infection. Emerging data suggests that specific characteristics of CD4 T cells, including their phenotype, function, and location, can have direct influence on their likelihood of being infected and depleted by HIV. The susceptibility of MTB- and CMV-specific CD4 T cells to HIV infection has been linked to specific characteristics of these cells [5–6] and differential depletion rates of these cells could be a determinant in the timing of reactivation of these pathogens during HIV infection. For other pathogens (e.g. HPV, Cryptococcus, Salmonella, HHV8, and others), it is not known whether the characteristics of the pathogen-specific CD4 T cells impact susceptibility to HIV infection and depletion. However, themes arise in the study of MTB- and CMV-specific CD4 T cells that might be more general. For example, cellular activation and proliferation might promote HIV infection whereas expression of CCR5 ligands and replicative senescence (as observed in CMV-specific CD4 T cells) might inhibit infection (Table 1). Many of the T cell characteristics that influence infectivity are linked to maturational phenotype, such as the differential expression of MIP-1β and IL-2 during cellular differentiation (figure 1)[5–6]. It is likely that in addition to direct effects of antigen load and persistence on pathogen-specific responses, the cytokine and co-signalling milieu induced by antigen-presenting cells are also important. We therefore propose a model in which antigen, innate microbial stimuli, DCs, and T cells interact to establish pathogen-specific CD4 T cell characteristics that will ultimately determine their susceptibility to, and risk of depletion by, HIV (Figure 2).

A better understanding of how pathogen-specific CD4 T cells with different characteristics are generated could also lead to better vaccines against HIV and opportunistic pathogens. Both CMV and mycobacteria (BCG) are being developed as potential HIV vaccine vectors [92–93]. Assuming the insert-specific responses will reflect the type of immunity induced to the vector, it can be expected that these vaccines will stimulate T cell responses of very different quality, that will impart very different the susceptibility of these T cells to HIV infection and depletion, thereby potentially affecting the efficacy of these vaccines.

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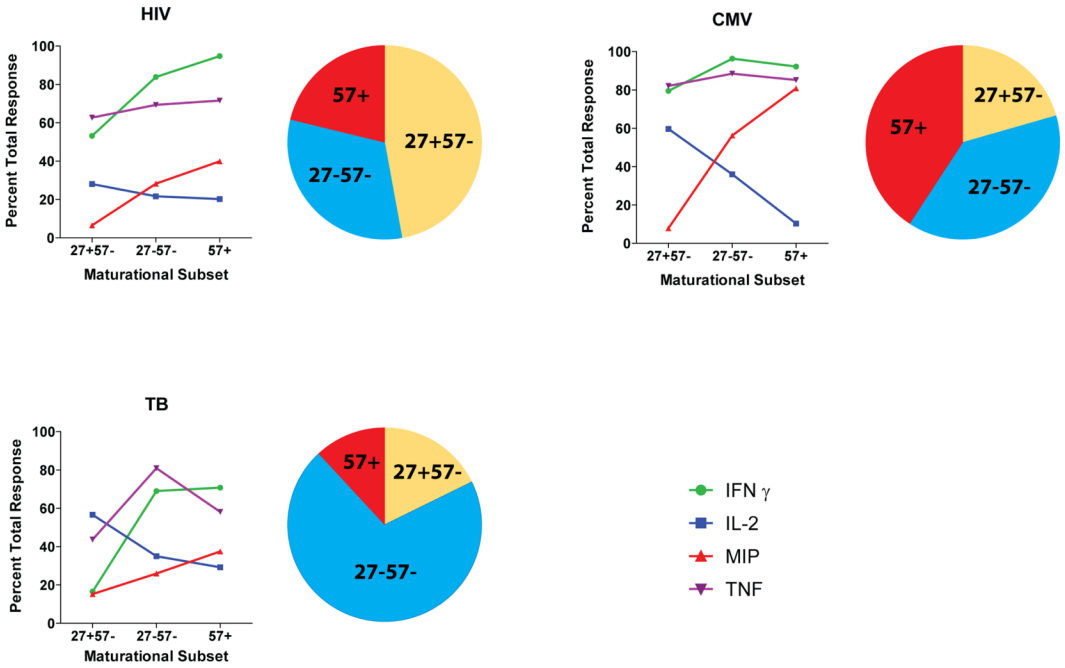

Figure 1. Maturation and function differences between pathogen-specific CD4 T cell populations

Each pie chart shows the maturational subsets delineated by CD27 and CD57 expression for different, circulating pathogen-specific CD4 T cell populations. The pathogen-specificity is indicated. Less mature CD4 T cells express CD27, more mature CD4 T cells express the senescence marker CD57. The line charts depict the capacity of each of these 3 maturational subsets to secrete IFNγ, IL-2, TNFα and MIP-1β. There are trends toward more MIP-1β and less IL-2 production which potentially reduces cellular HIV susceptibility with increasing maturity of pathogen-specific CD4 T cells. The data illustrated in this figure are based on [5–6] .

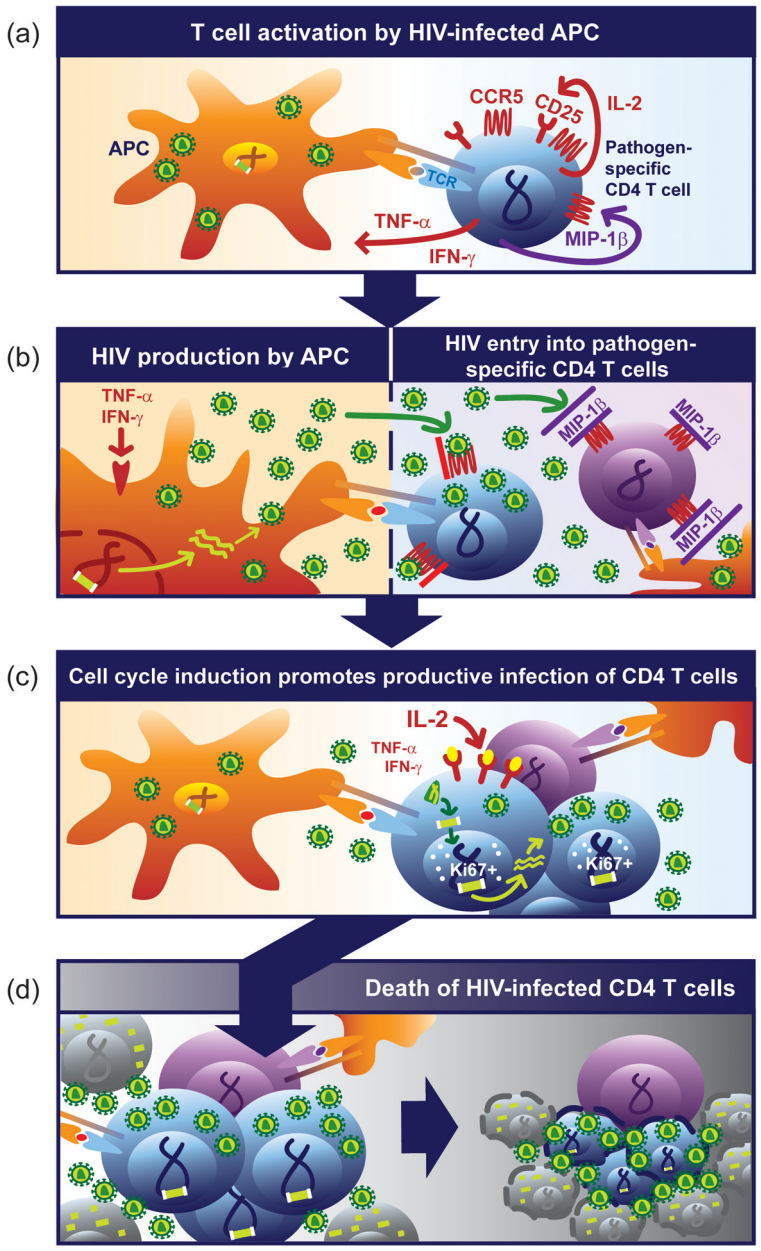

Figure 2. Proposed model for HIV-associated depletion of antigen-specific CD4 T cells

(a) Within secondary lymphoid tissue, a pathogen-specific CD4 T cell (blue) is activated by a HIV-infected antigen-presenting cell (APC, orange) upon recognition of its cognate peptide presented on MHC class II. T cell activation induces the secretion of pro-inflammatory cytokines and up regulation of the HIV co-receptor CCR5 (red) and CD25. More mature $CD57^{+}$ pathogen-specific CD4 T cells produce MIP-1β. **(b)** Pro-inflammatory cytokines, such as TNFα, promote HIV genomic transcription and production of virions by the APC, which are released into the interstitial space. HIV enters the T cell cytoplasm after binding its receptors CD4 and CCR5. Simultaneous production of MIP-1β (or other CCR5 ligands) by more mature pathogen-specific CD4 T cells can inhibit viral entry by blocking CCR5 entry. **(c)** IL2 signaling induces cell cycle induction within responding antigen-specific CD4 T cell expressing proliferation marker Ki67, and promotes complete reverse

transcription of the viral RNA Subsequently, viral cDNA is integrated into host genome. CD57+ CD4 T cells are refractory to cell cycle induction and do not promote complete reverse transcription of the viral RNA genome. Continuous presence of proinflammatory cytokines, such as TNFα, promote proviral transcription. **(d)** HIV infection of expanding pathogen-specific CD4 T cells culminates in death of a significant fraction of these pathogen-specific CD4 T cells. More mature pathogen-specific CD4 T cells producing MIP-1β (or other CCR5 ligands) survive.

Table 1

Phenotypic and functional markers that influence HIV infection

Putative cellular parameters associated with increased or decreased HIV susceptibility of antigen-specific CD4 T cells

Cellular marker	HIV infection	Comment
CD4	↑	HIV receptor
CCR5	↑	HIV receptor
CXCR4	↑	HIV receptor
α4β7	↑	HIV receptor
CD25	↑	Activation marker
HLA-DR	↑	Activation marker
Ki67	↑	Activation marker
IL2	↑	T cell growth factor
IL15	↑	T cell growth factor
CD57	↓	Senescence marker
MIP-1β/α Rantes	↓	CCR5 ligands