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Mucosal Immunity in HIV Controllers: The Right Place at the Right Time

Barbara L. Shacklett[1,2,*] and **April L. Ferre**[1]

[1]Department of Medical Microbiology and Immunology, School of Medicine, University of California at Davis, Davis, CA 95616

[2]Department of Medicine, Division of Infectious Diseases, School of Medicine, University of California at Davis, Davis, CA 95616

Abstract

Purpose of review—The phenomenon of long-term non-progression in HIV infection has been recognized for some time, and the ability of rare individuals, designated “elite controllers”, to control HIV in the absence of therapy is the focus of numerous ongoing studies. This review focuses on studies of HIV-specific immune responses in mucosal tissues as a potential correlate of immune control, with an emphasis on recently published work.

Recent findings—Genetic studies have implicated a role for elements localized to the major histocompatibility complex (MHC) on chromosome 6 in the immune control of HIV infection. In parallel, functional studies have strongly implicated MHC class I-restricted, CD8+ T-cell responses as a major contributor to elite control. In addition, the localization of HIV-specific CD8+ and CD4+ T-cells with respect to the major sites of virus replication in the body may be critical in determining clinical outcome.

Summary—Recent findings suggest that MHC class I-restricted, CD8+ T-cells are a major component of immune control in “elite controllers”. In addition, the presence of these effector cells at or near critical viral reservoirs, such as mucosal tissues, may be critical in determining their effectiveness at limiting viral replication and dissemination.

Keywords

Mucosal immunity; Gut; GALT; CTL; T-cell

Introduction

Typical HIV disease progression is marked by a decline in CD4+ T-cells and the loss of control of viral replication. However, a small subset of infected individuals are able to establish durable control of viral replication (elite controllers), and/or maintain relatively normal CD4+ T-cell counts for periods of 10 or more years (long-term non-progressors [LTNP]) in the absence of antiretroviral therapy (ART) [1,2]. Elite controllers and LTNP represent <1% and 10–15% of the HIV infected population, respectively [1,2]. Despite effective control of plasma viremia, elite controllers show heightened levels of immune activation compared to healthy controls, exhibit an increased incidence of comorbid inflammatory diseases such as atherosclerosis, and in rare cases may progress to AIDS [3,4].

*Corresponding Author: Barbara L. Shacklett, PhD, Associate Professor, Dept. of Medical Microbiology and Immunology, 3146 Tupper Hall, 1 Shields Ave., Davis, CA 95616 USA, Tel: (530) 752-6785, Fax: (530) 752-8692, blshacklett@ucdavis.edu.

Thus, while most elite controllers remain relatively free of overt HIV disease, they are not completely free from the consequences of immune activation and inflammation.

Mucosal tissues of the reproductive and gastrointestinal tracts serve as the major portals of entry for HIV. Gut-associated lymphoid tissue (GALT) is the largest lymphoid organ in the body, comprised of immune inductive sites (Peyer's patches and isolated lymphoid follicles) and effector sites in the lamina propria and epithelium (Figure 1). Because of its high density of CD4+ memory T-cells, most of which express HIV coreceptors CCR5 and CXCR4, the gut represents a major target for HIV infection. During the first weeks of infection, there is a rapid and profound loss of CD4+ T-cells from the intestinal lamina propria [5,6]. There is also considerable damage to epithelial integrity, resulting in "leaky gut" and translocation of bacterial products, such as lipopolysaccharide, into peripheral circulation [7,8]. Microbial translocation, leading to triggering of toll-like receptor signaling on cells of the immune system, has been implicated as a likely cause of the generalized activation that is a hallmark of chronic HIV infection [*9,**10]. Recent studies have highlighted the central role of the gastrointestinal mucosa as a reservoir for ongoing viral replication during chronic infection, the breakdown of gut epithelial barrier function and its relationship to immune activation, and finally, mucosal T-cell responses as a potential correlate of HIV control.

Mucosal T-cell responses in HIV controllers: CD8+/CD4+ T-cell synergy

In both HIV-infected individuals and healthy controls, CD8+ T-cells from the gastrointestinal tract express low levels of perforin as compared to their counterparts in blood [11]. Nevertheless, HIV-specific CD8+ T-cells are abundant in rectal mucosa of chronically infected individuals [12,13]. Following *in vitro* stimulation, these cells express a broad range of cytokines/chemokines (IFNγ, IL-2, MIP1-β, and TNFα) and the degranulation marker CD107 [14,15]. A study of rectal HIV Gag-specific CD8+ T-cell responses in 15 HIV-positive individuals not on highly-active antiretroviral therapy (HAART), with a broad range of viral loads and CD4+ T-cell counts, revealed a positive correlation between total response magnitude (i.e., percent Gag-responsive CD8+ T-cells), polyfunctionality (i.e., production of 3 or more effector molecules, also referred to as response "quality") and CD4+ T-cell count, as well as an inverse correlation between response magnitude and plasma viral load [15]. Thus, in this study, individuals with the highest blood CD4+ T-cell counts and lowest plasma viral loads had the strongest, most polyfunctional rectal CD8+ T-cell responses.

In a subsequent study, CD8+ T-cell responses from paired blood and rectal biopsy samples were obtained from 17 elite controllers (viral load [VL] <75 copies/mL), 11 viremic controllers (VL 75–2,000 copies/mL), 14 non-controllers (VL >10,000 copies/mL), and 10 HAART-treated subjects (VL <75 copies/mL) and assessed for their ability to degranulate and/or secrete multiple cytokines in response to HIV Gag stimulation [16]. There was considerable heterogeneity in all groups; however, mucosal CD8+ T-cell responses in controllers were significantly more robust and polyfunctional than in either non-controllers or HAART-suppressed individuals. Importantly, in this study there were no differences in the magnitude or quality of peripheral blood CD8+ T-cell responses between controllers and non-controllers. Additionally, controllers with "protective" class I HLA alleles (HLA-B13, B27, B57, B58, and B81) had significantly more polyfunctional mucosal Gag-specific CD8+ T-cells than controllers lacking these alleles, and showed a trend towards higher response magnitudes [16]. HIV controllers also had significant preservation of rectal CD4+ T-cells as compared to non-controllers. However, all HIV-positive groups had significantly lower rectal CD4+ T-cell percentages than seronegatives [16].

In a companion study, Ferre and colleagues evaluated Gag-specific CD4+ T-cell responses in rectal mucosa from the same patients [*17]. Controllers had significantly higher magnitude rectal CD4+ T-cell responses than patients on HAART, and the frequency of polyfunctional mucosal CD4+ T-cells was significantly greater in controllers than in either non-controllers or patients on HAART. Intriguingly, controllers with the strongest and most polyfunctional rectal CD4+ T-cell responses in this study possessed the HLA class II alleles HLA-DRB1*13 and/or HLA-DQB1*06 in addition to protective MHC class I alleles [*17]. Although this study was not statistically powered to distinguish the protective effects of MHC class I versus MHC class II alleles, an earlier report found an association between the HLA-DRB1*13/HLA-DQB1*06 haplotype, long-term nonprogression and strong p24-specific lymphoproliferative responses in the absence of any protective MHC class I alleles [18].

Taken together, these findings reveal that many HIV controllers, particularly those with “protective” HLA alleles, have strong, polyfunctional mucosal CD4+ and CD8+ T-cell responses that are not necessarily mirrored in blood. Additionally, both the magnitude and “quality” of mucosal CD4+ T-cell responses positively correlated with the strength of mucosal CD8+ T-cell responses. This suggests that mucosal CD4+ T-cell “help” supports the development and maintenance of robust CD8+ T-cell responses. Mucosal CD8+ T-cells, in turn, eradicate infected cells, thereby limiting *de novo* infection of CD4+ T-cells; accordingly, these two cell types likely act synergistically to limit virus production and preserve relatively high CD4+ T-cell frequencies in mucosal tissues of HIV controllers.

Gene expression analysis: distinct molecular signatures

Gene expression analyses of gastrointestinal tissue from controllers and non-controllers have also revealed molecular signatures of mucosal immunity that distinguish these two patient groups, while generally supporting an important role for mucosal cell-mediated immunity in HIV controllers [19,20]. Using microarray technology, Sankaran and colleagues studied gene expression profiles in blood and jejunal biopsies from four long-term nonprogressors, 15 ART-naïve HIV positive patients with VL >10,000 (i.e., non-controllers), and 8 seronegative controls [19]. Non-controllers showed increased expression of genes regulating immune activation, leukocyte trafficking, and inflammation as compared to patients characterized as long-term nonprogressors. As compared to healthy controls, both LTNP and non-controllers showed decreased expression of genes associated with nutrient absorption and lipid metabolism, suggesting significant effects of HIV infection on gastrointestinal function even in non-progressors.

In a more recent study, Loke and colleagues used a combination of flow cytometry assays and oligonucleotide expression arrays to compare gene expression in blood and rectosigmoid biopsies from 9 HIV controllers and 11 non-controllers [20]. Genes whose expression was strongly associated with controller status included those involved in T-cell immunity, MHC class I and II-related immunity, NK-cell responses, and cytokines/chemokines. Although mucosal HIV-specific immune responses were not measured, rectal CD4+ T-cells were tested for the ability to respond to polyclonal stimulation (PMA + Ionomycin) by producing cytokines such as IL-2, IFN-γ, TNF-α and IL-17. Notably, the ability of mucosal (but not blood) CD4+ T-cells to secrete multiple cytokines was strongly associated with high peripheral CD4+ T-cell count and controller status. There was a strong relationship between expression of markers of immune activation (e.g., CD38) in blood and rectal mucosa; the frequency of CD4+Foxp3+ putative Treg cells was also strongly associated with immune activation. These findings suggested that measurements of immune activation in blood are often reflective of those in mucosa, and might be used as surrogates to infer mucosal immune activation when gut biopsies are not available. The conclusions

from this study also supported the hypothesis that mucosal CD4+ T-cell responses contribute significantly to immune control [20].

Targeting conserved, functionally constrained regions of Gag

In addition to the strength and "quality" of mucosal T-cell responses, the targeting of T-cell epitopes located in highly conserved regions of the viral proteome appears to be important for viral control. Extensive studies have characterized the immunodominant HIV epitopes restricted by HLA-B57 and HLA-B27 and recognized by CD8+ T-cells in blood. In the case of HLA-B27, a single immunodominant epitope in the capsid protein (p24), KK10, is typically recognized by cytotoxic T-cells (CTL) [21,22]. This epitope is located in a structurally constrained region involved in interactions between the viral capsid and the host protein cyclophilin A [21,22]. Viral escape from KK10-specific CTL frequently occurs late in infection and is associated with progression to AIDS. In the case of HLA-B57, four immunodominant epitopes are located within p24. One of these, TW10, is targeted by CTL early in infection and is also presented by HLA-B58, a close relative of B57. CTL escape mutations in TW10 occur rapidly and have a negative impact on viral fitness during the acute/early phase of infection; in addition, many escape variants also elicit strong CTL responses [**23–**27]. Thus, the combination of reduced viral fitness and strong CTL responses likely contributes to immune control.

Because the immunodominant HLA-B57 and B27-restricted epitopes were initially characterized using CTL from blood, it was important to determine whether these epitopes were also recognized by T-cells in mucosal tissues. Ferre and colleagues mapped CD8+ T-cell responses to HIV Gag, Env and Nef peptides in blood and rectal mucosa from 30 controllers and 14 non-controllers [*28]. Mucosal CD8+ T-cells from controllers more frequently targeted conserved regions in HIV Gag p24 and the zinc-finger domains of Gag p7, while those from non-controllers preferentially targeted Nef. Immunodominant CD8+ T-cell responses, including those directed towards KK10 and TW10, were shared between blood and rectal mucosa. Among controllers, mucosal CD8+ T-cell responses to HLA-B27 and -B57 restricted epitopes were consistently of greater magnitude than responses to other epitopes. Interestingly, mucosal CD4+ T-cells from controllers with HLA-DRB1*13 and/or HLA-DQB1*06 were also shown to target epitopes within p24 that overlap with immunodominant HLA-B27 and -B57 restricted epitopes [*17]. Thus, mucosal CD8+ and CD4+ T-cells from controllers preferentially target conserved, structurally constrained regions of the HIV Gag protein. The breadth of mucosal CD8+ T-cell responses (i.e., number of epitopes recognized) did not differ significantly between controllers and non-controllers. Thus, the total number of epitopes recognized may not be as critical as the targeting of specific conserved viral sequences, where escape mutations elicit a strong cost in viral fitness.

Mucosal tissues as a viral reservoir in HIV/SIV controllers

Although Elite Controllers are defined as having plasma viral loads below the limit of detection by standard assays, at least four studies have demonstrated that controllers harbor low levels of plasma viral RNA that may be detected using ultrasensitive methods [29–32]. Dinoso and colleagues measured viral RNA using an ultrasensitive RT-PCR based assay after concentrating virus from 7 mL of plasma by ultracentrifugation. They reported that 9 of 14 elite controllers had undetectable plasma viral loads using this method, as compared to 6 of 15 individuals on suppressive HAART [29]. Using a transcription-mediated amplification (TMA) assay with a 50% detection limit of 3.6 to 14 viral RNA copies/mL plasma, Hatano and colleagues found that 45 of 46 controllers harbored detectable HIV RNA [30]. Strikingly, 15 subjects had detectable HIV RNA at all time points tested, and most also had cell-associated HIV RNA and proviral DNA. Median plasma HIV RNA levels were higher

in Elite Controllers than in a comparison group of HAART-suppressed patients, although this difference did not reach significance.

To date, no studies have systematically addressed levels of HIV RNA and DNA in mucosal tissues of HIV controllers using ultrasensitive methods. However, the robust HIV-specific T-cell responses detected in rectal mucosa of controllers suggest ongoing viral replication in these tissues, since such responses rapidly wane in patients on HAART [16,*17]. Several recent studies have quantified mucosal viral load in patients on HAART with well-suppressed viremia. A seminal study by Chun and colleagues revealed that HIV DNA persists in terminal ileum of patients on long-term successful HAART [33], despite plasma viral loads below 50 copies/ml. Furthermore, phylogenetic analysis of viral envelope (C2-V5) DNA sequences provided evidence for cross-infection of CD4+ T-cells from blood and gut, rather than strict anatomic compartmentalization. A subsequent study by Yukl and colleagues extended these findings to four tissue sites: duodenum, ileum, ascending colon, and rectum in 8 patients on ART with viral loads <40 copies/ml [34]. In this study, HIV DNA levels were significantly higher in ileum, colon and rectum than in PBMC, and median HIV RNA levels were highest in terminal ileum. Taken together, these studies demonstrate that the gastrointestinal mucosa remains an important reservoir for HIV DNA and RNA even in the absence of detectable plasma viremia. Studies of HIV controllers will likely reveal similar findings.

Among nonhuman primate models for AIDS, rhesus macaques of Chinese origin (ChRh) are relatively resistant to disease progression when infected with SIVmac; although the majority of infected macaques eventually develop simian AIDS, approximately 30% maintain low viral loads for at least 5–6 years [35–37]. Ling and colleagues have used this model to study mucosal CD4+ T-cell depletion and reconstitution in controllers, as well as viral replication and compartmentalization in the GI tract. In a recent study of nine ChRh inoculated with pathogenic SIVmac239, three animals spontaneously controlled viremia [36]. Like typical progressors, these SIV controllers experienced acute phase viremia and profound jejunal CD4+ T-cell depletion at two to four weeks post-infection. However, unlike progressors, controllers showed gradual restoration of intestinal CD4+/CCR5+ T-cells beginning at 2 months post-infection. *In vivo* depletion of CD8+ T-cells in two controllers led to transient viremia in both animals and the development of simian AIDS in one, implying a major role for CD8+ T-cells in controlling virus replication. Notably, the animal that developed AIDS failed to fully reconstitute intestinal CD8+ T-cells following antibody-mediated depletion.

In a follow-up study, Ling and colleagues used the ChRh model to quantify viral replication in both small and large intestine of SIV controllers [35]. Five of 7 controllers had fewer than 10 viral RNA copies/10^6 PBMC. However, controllers consistently harbored cell-associated viral RNA in colonic mucosa (mean 767 vRNA copies/10^6 cells) and associated mesenteric lymph nodes (mean 486 vRNA copies/10^6 cells). These findings indicate that the gastrointestinal mucosa remains a major SIV reservoir even in controllers lacking detectable plasma viremia. In particular, colonic mucosa may be particularly susceptible to SIV/HIV infection due to the high frequency of target cells that are CD4+CCR5+ and have a “memory” phenotype [35].

Conclusions

A growing consensus from genomics and cellular immunology studies points to a major, although clearly not exclusive, role for cell-mediated immune responses in establishing and maintaining HIV controller status [38–42]. Furthermore, seminal studies of acute SIV infection point to the importance of *in vivo* effector-to-target ratio in determining the outcome of the “race between expansion of infection and the immune response generated to contain it” [43]. Recent studies have revealed that the gastrointestinal mucosa remains an

important reservoir for viral replication even in individuals with viral load suppressed through HAART, and in SIV-infected macaques that control infection without therapy. Furthermore, the magnitude and quality of HIV-specific mucosal T-cell responses appear to correlate positively with controller status. Taken together, these findings support the view that T-cell responses occurring at the “right place and time”, i.e., in the gastrointestinal tract during chronic (and perhaps also acute) infection, may be a major component of HIV control.

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Key Points

- A growing consensus from genomics and cellular immunology studies points to a major role for cell-mediated immune responses in establishing and maintaining HIV controller status.
- The gastrointestinal mucosa remains an important reservoir for viral replication even in individuals with viral load suppressed through HAART, and in SIV-infected macaques that control infection without therapy.
- The magnitude and quality of HIV-specific mucosal T-cell responses appear to correlate positively with controller status.
- T-cell responses occurring at the “right place and time”, i.e., in the gastrointestinal tract during chronic, and likely also acute infection, may be a major component of HIV control.

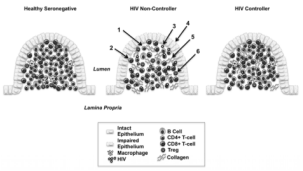

Figure 1.

The Figure shows idealized drawings of rectal mucosa in uninfected individuals (left), HIV non-controllers (NC, center), and HIV controllers (C, right). Individual cell types are identified in the legend. For simplicity, innate effector cells such as natural killer (NK) cells and TCR-gamma delta cells are not shown. Major differences between groups include: (1) CD4+ T-cells are severely depleted in NC, but relatively well preserved in C. Mucosal CD4+ T-cells in C (but not NC) include significant populations of HIV-specific, polyfunctional cells that act in synergy with CD8+ T-cells. (2) CD8+ T-cells are abundant in both NC and C, but the proportion of HIV-specific, polyfunctional CD8+ T-cells is higher in C. (3) HIV virus production is high in the GI tract of NC; however, despite low levels of plasma viremia, controllers likely also have detectable virus in gut tissue, as suggested by studies in the SIV model. (4) Intestinal epithelial barrier integrity is severely compromised in NC, but to a much lesser extent in C. (5) Immune activation leads to deposition of collagen in lymphoid tissues of NC, potentially limiting CD4+ T-cell reconstitution. Controllers also have elevated markers of immune activation as compared to HIV negative individuals, but significantly lower than NC. (6) Regulatory T-cells are positively correlated with immune activation, and are present at higher frequency (as % of total CD4+ T-cells) in NC than C. In summary, these three groups represent a continuum with HIV controllers showing less barrier impairment, lower immune activation, and stronger, more polyfunctional HIV-specific T-cell responses than non-controllers.