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Mucosal Immunity in HIV/SIV Infection: T Cells, B Cells and Beyond

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Abstract

As our understanding of mucosal immunity increases, it is becoming clear that the host response to HIV-1 is more complex and nuanced than originally believed. The mucosal landscape is populated with a variety of specialized cell types whose functions include combating infectious agents while preserving commensal microbiota, maintaining barrier integrity, and ensuring immune homeostasis. Advances in multiparameter flow cytometry, gene expression analysis and bioinformatics have allowed more detailed characterization of these cell types and their roles in host defense than was previously possible. This review provides an overview of existing literature on immunity to HIV-1 and SIVmac in mucosal tissues of the female reproductive tract and the gastrointestinal tract, focusing on major effector cell populations and briefly summarizing new information on tissue resident memory T cells, T_{reg}, Th17, Th22 and innate lymphocytes (ILC), subsets that have been studied primarily in the gastrointestinal mucosa.

Keywords

HIV-1; SIV; mucosa; gut; T-cell; adaptive; innate

1. INTRODUCTION

Mucosal tissues house a majority of the body's lymphocytes, including the CD4+ T cells that serve as the primary targets for HIV-1 infection. The reproductive and gastrointestinal mucosal tissues are the major portals of entry for HIV-1. Over the past decades, numerous studies have explored the immune responses occurring at these tissue sites, with results underscoring the concept that the balance between inflammation and protective immunity is established at or near these portals of entry. While many aspects of mucosal immunity remain to be fully elucidated, these efforts have revealed important new insights into the innate and adaptive immune cells housed within mucosal tissues, including trafficking

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patterns, regulation of effector functions, induction of memory, and functional plasticity. What follows is a summary of this literature, with an emphasis on recent developments.

2. THE FEMALE REPRODUCTIVE TRACT

2.1. The Female Reproductive Tract: Which Sites Are Most Important for Immune Defense?

The vast majority of HIV-1 infections result from sexual contact via the genital tract or the anorectal canal. Women account for roughly half of the estimated 36-37 million persons living with HIV-1 infection worldwide. HIV-1 acquisition via the female reproductive tract (FRT) is believed to be less efficient than transmission via the anorectal mucosa, an interpretation supported by experimental infection studies in rhesus macaques [1]. The lower FRT, which includes the vagina and ectocervix, is shielded from infection by a relatively thick, stratified squamous (type II) epithelium [2]. In contrast, the upper FRT, which includes the endocervix and uterinendometrium, is lined with simple columnar (type I) epithelium. These two tissues meet at the cervical transformation zone, an area rich in potential HIV-1 target cells such as $CD4^+$ T cells and antigen-presenting cells [3]. Cervical mucus, which helps protect the upper tract, varies in volume, composition and physical characteristics throughout the menstrual cycle [4], becoming a thick “mucus plug” during pregnancy [5].

The majority of HIV-1 infections in women are believed to occur *via* the lower FRT, a concept supported by experimental inoculation studies of rhesus macaques with simian immunodeficiency virus (SIVmac) [6, 7]. Hysterectomized macaques are susceptible to productive infection following intravaginal exposure [8], and a randomized clinical trial revealed no reduction in HIV-1 acquisition among women using a diaphragm (which blocks access to the upper FRT) compared to controls [9]. Proposed mechanisms by which HIV-1 may enter the body through the lower FRT include disruption of the mucosal surface through micro-breaches occurring during sexual intercourse; disruption due to inflammation or ulceration associated with other sexually transmitted infections; uptake of virus by Langerhans’ cells or dendritic cells within or directly below the epithelium; and direct infection of $CD4^+$ T cells or macrophages within the epithelium [10–14]. In a recent study, $CCR6^+$ $CD4^+$ T cells of the Th17 lineage were identified as the primary targets of SIV during vaginal transmission [15], extending previous studies showing high susceptibility of this subset to HIV-1 infection *in vitro* [16].

Although HIV-1 transmission clearly can and does occur via the lower FRT, susceptible target cells are present throughout the upper and lower tract [14, 17]. The extent to which the upper FRT serves as a target and/or reservoir for HIV-1 replication is not known. $CD4^+$ T cells in the upper FRT express CCR5 and exhibit an activated memory phenotype [17]. In experimental infection studies of rhesus macaques using SIVmac, tissues of the upper tract, including the ovary, were shown to become infected following intravaginal exposure [18]. *In vitro* studies have also demonstrated susceptibility of ovarian $CD4^+$ T cells to infection with laboratory-adapted HIV-1 strains [19]. However, imaging studies in women undergoing simulated intercourse, utilizing radiolabeled surrogates for cell-free and cell-associated virus, did not reveal migration of the surrogates to the upper FRT [20]. *In vitro,* endometrial

macrophages and T cells are permissive to HIV-1 infection; however, endometrial and decidual macrophages express the HIV-1 restriction factor SAMHD1, which may restrict their susceptibility to productive infection *in vivo* [21, 22]. To date, few studies have addressed the extent to which $CD4^+$ T cells in the upper FRT are infected *in vivo* [23]. In summary, then, further studies are needed to fully address the role of the upper FRT in HIV-1 transmission, replication and pathogenesis.

2.2. Antigen-Specific T-cell Responses in the FRT

Comprehensive studies of immune responses in the human FRT present significant logistical challenges, and are therefore rare in the literature. However, several groups have investigated adaptive responses in rhesus macaques experimentally infected with SIVmac, and to a lesser extent in HIV-1-infected women. Mucosal $CD8^+$ T-cell responses to SIVmac emerge in the cervicovaginal mucosa with kinetics that are “too little and too late” to prevent viral dissemination to draining lymph nodes [24]. Coupled with observations from murine lymphocytic choriomeningitis virus infection, this finding has suggested that vaccine-mediated induction of a sizable population of HIV-1-specific T cells in the FRT might provide protection against vaginal exposure [25, 26]. However, it has proven challenging to induce sufficiently large populations of antigen-specific T cells at mucosal ‘front lines’ to allow direct testing of this hypothesis.

During chronic infection, HIV-1-specific $CD4^+$ and $CD8^+$ T cells are detected in the cervix and vagina. In early studies, SIVmac-specific cytotoxic T cells (CTL) were identified in vaginal tissues of infected rhesus macaques [27], and HIV-1-specific CTL activity was detected by ^{51}Cr release assay in polyclonally expanded cervical T cells from HIV-1-positive women [28, 29]. Comparison of MHC restriction, TCR CDR3 region sequences, and epitopes recognized by CTL from cervix and blood revealed that certain T-cell clones were indeed found at both sites, suggesting that some HIV-1-specific T-cell clones are widely distributed throughout the body rather than restricted to tissue residency [28, 29].

A series of more recent studies, conducted among South African women with HIV-1, focused on cervical $CD8^+$ T-cell responses, their relationship to cervical inflammation, and their role in limiting viral shedding in cervical secretions [30–32]. Gumbi and colleagues [33] studied the relationship between local inflammation and HIV-1 Gag-specific responses in $CD8^+$ T cells from cervical cytobrush. They detected no relationship between the magnitude of cervical responses and virus shedding in genital secretions, implying that cervical T-cell responses are often ineffective at containing viral replication. Women who were shedding virus in cervical secretions had higher concentrations of proinflammatory cytokines (TNFα, IL-1β, IL-6, and IL-8) in secretions than non-shedders, suggesting that genital inflammation may promote HIV-1 replication and shedding within the cervical mucosa [33].

T-cell “polyfunctionality”, i.e., the ability to respond to T-cell receptor stimulation by producing multiple effector cytokines, chemokines and cytolytic granule constituents, has been associated with control of HIV-1 replication in Elite Controllers, who maintain low to undetectable viral load without antiretroviral therapy [34, 35]. Investigating cervical HIV-1 Gag-specific T cells in a South African cohort, Bere and colleagues [36] found that these

cells were predominantly monofunctional. Polyfunctional cervical T cells were sometimes detected in women with relatively high blood $CD4^+$ T-cell counts and low plasma viral loads, but the presence of polyfunctional T cells did not prevent HIV-1 shedding from the genital tract [36].

Nkwanyana and colleagues [37] explored the phenotype of cervical T cells from HIV-1 infected women. $CD4^+$ T cells were relatively depleted, most $CD8^+$ T cells had an effector memory phenotype, and T cell counts were positively correlated with concentrations of proinflammatory cytokines [37]. Mkhize and colleagues [38] studied the effects of highly active antiretroviral therapy (HAART) on cervical $CD4^+$ T-cell reconstitution and HIV-1 viral load suppression in cervical secretions. Their work revealed a significant association between genital HIV-1 shedding and viral RNA levels in blood, both of which were well suppressed in HAART-compliant women. However, HIV-1-specific $CD8^+$ T-cell responses in blood were greatly reduced following HAART, while those in the cervix were maintained. This finding may suggest that suboptimal drug concentrations were present in the lower FRT, allowing for low-level or intermittent viral persistence that would stimulate memory T-cell responses [38].

2.3. Reproductive Hormones and Adaptive Immunity in the FRT

Reproductive hormones impact many features of the FRT, including the composition, thickness and abundance of genital mucus [39]; the composition of vaginal microbiota [39]; the thickness of the vaginal epithelium in nonhuman primates [40]; and the presence and activity of immune effector cells and molecules of innate immunity [41]. The effects of hormonal contraceptives on the FRT, and implications for HIV-1 susceptibility, have become the subject of considerable study and debate. Two recent meta-analyses concluded that women using the long-lasting injectable contraceptive depot-medroxyprogesterone acetate (DMPA) face a 40-50% greater risk of HIV-1 acquisition compared to controls [42, 43]. The mechanisms underlying this enhanced risk are incompletely understood, but may include increased target cell density; increased HIV-1 coreceptor expression; thinning of the epithelial barrier; and/or changes in the vaginal microbiome [44–47]. The question of enhanced susceptibility promises to remain a topic of active investigation, with important implications for public health policy.

Tissues of the upper and lower FRT respond differently to cyclic hormonal fluctuations during the menstrual cycle [48, 49]. In the lower tract (ectocervix and vagina), cytotoxic T-cell activity remains relatively constant throughout the menstrual cycle. However, levels of immunoglobulins (IgG and IgA) in cervical secretions decline after ovulation, rebounding near the end of the cycle [41]. Similar patterns have been observed for soluble factors of innate immunity (e.g., lactoferrin, SLPI and HBD2), suggesting that the post-ovulatory phase, termed the secretory or luteal phase, represents a window of vulnerability to HIV-1 and other sexually transmitted pathogens for the lower reproductive tract [48, 49].

In the upper FRT, adaptive T-cell responses vary through the menstrual cycle: $CD8^+$ T cells isolated from proliferative phase endometrial tissue show strong cytotoxic activity in ^{51}Cr release assays; however, T cells isolated during the secretory phase show reduced activity [48, 49]. Thus, antigen-specific T-cell responses are suppressed in the upper tract during the

secretory phase, reinforcing the notion of a “window of opportunity” for pathogens. Other changes affect the distribution of endometrial T cells: during the proliferative phase, $CD8^+$ T cells localize to lymphoid aggregates located in the lamina basalis of the uterine endometrium [50, 51]. The function of these structures is not known, but they may serve to promote retention of resident memory T cells during menstrual shedding [41]. HIV-1-specific T-cell responses in the upper FRT have not been extensively characterized [52], nor has the impact of the menstrual cycle on these responses been fully explored to date.

3. THE GASTROINTESTINAL TRACT

3.1. The Gastrointestinal Tract as a Portal of HIV-1 Entry

The gastrointestinal (GI) tract is the largest lymphoid organ in the body, as well as a major physical and immunological barrier against infectious pathogens. In the early years of the HIV/AIDS epidemic, diarrhea and wasting syndromes were among the most commonly reported features of the disease, although the reasons for this were initially unclear. Research later revealed that the GI tract houses $CD4^+$ T-cell subsets that are highly susceptible to HIV-1 infection, and are among the first cells in the body to be depleted regardless of the route of HIV-1 transmission [53]. Subsequent work provided evidence linking acute HIV-1 infection to gut epithelial damage and microbial translocation, contributing to the generalized immune activation associated with HIV-1 disease [54, 55].

Transmission studies in rhesus macaques suggest that anal intercourse is significantly more likely than vaginal intercourse to result in HIV-1 acquisition by the receptive partner[1]. The upper anorectal canal is lined with simple columnar (type I) epithelium; the lower canal is lined with stratified squamous (type II) epithelium. These are separated by the dentate (or pectinate) line and a narrow zone of transitional epithelium [56]. HIV-1 target cells are abundant in the distal GI tract [57–59]. During receptive anal intercourse, HIV-1 transmission may occur through several mechanisms: epithelial microabrasions or breaches; transcytosis across epithelial cells; or virion capture by mucosal dendritic cells (reviewed in [60]). Recent studies have used SPECT/CT imaging of radiolabeled surrogates to model dissemination of viral particles in the anorectal canal during simulated intercourse. Radiolabeled surrogates reached peak levels at 10-20 cm from the anal verge, near the rectosigmoid junction [61]. Although under-studied in this context, the anorectal mucosa should not be overlooked as a potential portal of entry for HIV-1 in heterosexual women. A recent meta-analysis suggested significant prevalence and frequency of anal intercourse among heterosexual women in a wide range of cultures and environments [62, 63].

The susceptibility of the GI tract to HIV-1 infection, along with the relative accessibility of tissue sampling in this compartment, have made possible a wide range of detailed studies designed to elucidate the role of individual immune cell subsets in the host response to HIV/SIV. The remainder of this section presents a summary of major findings, organized by immune cell type.

3.2. Gastrointestinal CD8+ T Cells and HIV-1 Infection

The literature describing $CD8^+$ T-cell responses to HIV-1 infection is considerable; however, the vast majority of studies have focused on T cells isolated from blood. Early mucosal studies of individuals with chronic HIV-1 infection who were also seropositive for cytomegalovirus (CMV) revealed that HIV-1-specific $CD8^+$ T cells could be detected in rectal and duodenal biopsies, while CMV-specific $CD8^+$ T cells, though abundant in blood, were rare in these tissues [64–66]. Polyclonally expanded rectal $CD8^+$ T cells were demonstrated to kill HIV-1 antigen-pulsed target cells in ^{51}Cr release assays [29, 65]. Mapping of HIV-1-specific $CD8^+$ T-cell epitope recognition, using pooled peptides, revealed that mucosal responses tended to mirror those in blood, at least in antigenic specificity [67]. With the advent of multiparameter flow cytometry, protocols were developed to measure T-cell production of multiple cytokines, chemokines, and cytolytic granule constituents. These approaches prompted attempts to identify immunologic correlates of viral clearance. Studies of individuals with chronic HIV-1 infection and a range of viral loads and $CD4^+$ T-cell counts revealed that strong, polyfunctional HIV-1 Gag-specific responses in rectal mucosa were frequently associated with well-preserved mucosal $CD4^+$ T-cell populations and low plasma viral load [68, 69]. Individuals meeting the definition of ‘HIV controllers’ had significant preservation of mucosal $CD4^+$ T cells, as well as strong, polyfunctional HIV Gag-specific $CD8^+$ [34, 70] and $CD4^+$ [71] T-cell responses in rectal mucosa. Many, but not all of these controllers possessed the MHC class I alleles HLA-B*57 and/or B*27. Taken together, these findings supported the widely held interpretation, later confirmed by genome-wide association studies [72, 73], that MHC-restricted T-cell responses account for a significant component of the “elite controller” phenomenon, and further suggested that T-cell populations residing in the GI tract contribute to this immune control [34].

3.2.1. Are Gastrointestinal CD8+ T Cells “Dysfunctional” for Cytotoxicity?—

MHC class I restricted, $CD8^+$ T cells, which release cytolytic granules upon T-cell receptor (TCR) stimulation, have generally been considered to act primarily by killing infected host cells. Accordingly, the terms $CD8^+$ T cell and cytotoxic T cell (CTL) are often used interchangeably. However, close examination of gastrointestinal $CD8^+$ T cells revealed that these cells contain significantly less perforin and granzyme B than their blood counterparts, regardless of HIV-1 infection status [74]. This deficit was most evident in rectal effector memory (T_{EM}) and terminally differentiated effector (T_{EMRA}) $CD8^+$ T-cell subsets, whose blood counterparts contain the highest levels of perforin and granzyme B [75]. Furthermore, rectal $CD8^+$ T cells from both healthy and HIV-1-infected individuals were significantly less able than blood $CD8^+$ T cells to kill GFP-labeled P815 target cells in a redirected lysis assay [75]. Finally, two transcription factors whose expression is required for perforin expression and cytotoxicity, T-bet and Eomesodermin (Eomes), are weakly expressed by rectal $CD8^+$ T cells [75]. These observations are consistent with the recently described tissue resident memory subset (T_{RM}), described below. Taken together, these findings suggest that the predominant antiviral functions of rectal $CD8^+$ T cells involve release of HIV-1-blocking chemokines and immunomodulatory cytokines, with cytotoxic killing of infected $CD4^+$ T cells playing a secondary role [75]. We speculate that tissue-specific limitation on cytotoxic activity (i.e., low perforin and granzyme expression) might prove beneficial to the host by limiting mucosal T-cell depletion and tissue damage; however, in the case of chronic viral

infection such as HIV-1, the inability to fully eradicate infected cells likely also contributes to the role of the GI tract as a viral reservoir. It is tempting to suggest that approaches designed to stimulate more effective mucosal cytotoxic T-cell responses, either by increasing their abundance or by "programming" them for greater cytotoxic capacity, might provide more effective first-line protection against mucosal infections, and/or promote better pathogen clearance from tissues in the context of chronic infection [26, 75]

3.2.2. Tissue Resident Memory T Cells (T_{RM}): A Unique Role in Antiviral Host Defense—Until recently the dominant paradigm for T-cell differentiation suggested that activated effector T cells migrate continuously throughout the host, searching for and responding to local tissue infection. However, extensive studies in mice revealed that effectors entering certain tissues, including the gastrointestinal tract, are induced to differentiate into "tissue resident" cells by exposure to locally produced cytokines including TGFβ, IL-15, IL-33 and TNFα [76–83]. T_{RM} exhibit a distinct cell surface phenotype, with expression of αEβ7 integrin/CD103, CD69, and downregulation of CD62L, CCR7 and S1PR1 [84]. In contrast to short-lived effector cells, which express T-bet, and lymphoid-localized central memory cells, which express Eomesodermin, T_{RM} are typically T-bet^{Low} and Eomes^{Neg}. This corresponds to the phenotype previously observed to be abundant in rectal mucosal $CD8^+$ T cells from HIV-1^+ and healthy individuals [75, 82, 85].

Given that T_{RM} in mouse models play important roles in triggering innate immune responses and recruiting other immune cells to sites of infection, it will be important to clarify the contribution of T_{RM} to HIV-1 clearance in humans. As stated above, a more nuanced understanding of the role of mucosal $CD8^+$ T cells in fighting viral infection may inform attempts to purge mucosal tissues of residual HIV-1 replication, particularly in the context of therapeutic vaccination and the 'HIV Cure' initiative.

3.3. Gastrointestinal $CD4^+$T Cells and HIV Infection

As discussed extensively elsewhere, gastrointestinal $CD4^+$ T cells are a major target for HIV/SIV infection and depletion during the acute phase of infection [86–89]. This depletion occurs rapidly, regardless of the initial infection route [53]. The mechanisms driving this phenomenon include direct viral infection [88] and apoptosis of uninfected bystander cells [87], as well as disruption of mucosal homing pathways involving integrin and chemokine expression [90, 91]. Initiation of antiretroviral therapy during acute HIV infection can partially preserve and/or restore mucosal $CD4^+$ T-cell populations; specific findings have varied by study [92–95].

3.3.1. Th17 Cells—Th17 cells appear to be preferentially infected and depleted in the GI tract during acute HIV/SIV infection [96]. In addition to IL-17, these $CD4^+$ T cells produce IL-22, IL-21, and are important for maintaining epithelial integrity and defense against extracellular bacteria and fungi [96]. In humans, Th17 differentiation requires transcription factor RORγt and exposure to polarizing cytokines including IL-23 [97]. Th17 cells are preferentially lost in hosts with pathogenic lentivirus infection (HIV-1 infected humans; SIVmac infected rhesus macaques), but not from hosts with nonpathogenic infection (sooty

mangabeys infected with SIVsm; African green monkeys) [96]. Individuals characterized as HIV-1 longterm nonprogressors also have intact mucosal Th17 populations [98].

Early loss of intestinal Th17 cells is associated with impairment of the gut epithelial barrier, promoting microbial translocation and chronic immune activation. In macaques, loss of Th17 cells as a result of SIVmac infection is associated with reduced immune control of *Salmonella enterica* serovar Typhimurium [99]. However, initiation of HAART during early acute HIV-1 infection (Fiebig I/II stages) leads to relative preservation of mucosal Th17 cells and reversal of systemic immune activation [95].

Using cells isolated from human blood to explore Th17-polarized subsets in greater detail than could be attempted with mucosal biopsies, Gosselin and colleagues [100.101] demonstrated that Th17-like cells with the phenotypes $CCR4^+/CCR6^+$ and $CXCR3^+/CCR6^+$ are highly permissive to HIV-1 infection *in vitro.* In colonic mucosa and blood of HIV-1-infected individuals on ART with undetectable plasma viremia, memory $CD4^+$ T cells expressing CCR6 were found to be enriched for replication-competent HIV DNA [102]. $CD4^+$ T cells activated under Th17-polarizing conditions reportedly have diminished expression of RNAses that can inhibit HIV-1 replication [103]; this may partly explain the increased susceptibility of such cells to HIV/SIV infection.

3.3.2. Regulatory T Cells—Regulatory T cells (T_{reg}) limit activation and effector functions of multiple immune cell types [104]. Their role is to restrict potentially harmful functions of autoreactive cells that have escaped central tolerance, as well as to limit ‘collateral damage’ that can arise as a consequence of normal pathogen-specific immune responses [104]. T_{reg} are identified by expression of the high-affinity interleukin-2 (IL-2) receptor alpha chain, CD25, and the transcription factor Foxp3. In chronic infections such as HIV-1, which require long-term commitment of adaptive immune ‘resources’, T_{reg} may inappropriately dampen the host response, favoring pathogen persistence. Similar to the classical Th1/Th2 paradigm describing a reciprocal relationship between two $CD4^+$ T-cell lineages with complementary functions, T_{reg} and Th17 are derived from a common progenitor and their differentiation is determined by cytokines produced by antigen-presenting cells in response to microbial products [105].

Studying $HIV\text{-}1^+$ controllers and non-controllers, Shaw and colleagues [106] found that the frequency of T_{reg} in rectal mucosa positively correlated with plasma viral load and expression of T-cell activation markers. Thus, HIV-1-positive individuals with high viral load and immune activation had high T_{reg} frequencies in mucosa. Mucosal T_{reg} in chronic HIV-1 infection maintained their capacity to suppress proliferation of autologous non-T_{reg} cells [106], suggesting that T_{reg} may contribute to suboptimal HIV-1-specific T-cell responses and, by extension, to viral persistence. In a cohort of Colombian HIV-positive subjects, HAART treatment significantly decreased, but did not normalize, T_{reg} frequency in rectal mucosa compared to seronegatives [107]. Exploring the mechanisms driving T_{reg} expansion in tissues of SIV-infected rhesus macaques, Presicce and colleagues [108] found that mature myeloid dendritic cells (mDCs) from spleen and mesenteric lymph nodes efficiently induced ‘conversion’ of autologous non-T_{reg} to $Foxp3^+$ T_{reg}.

3.3.3. The T_{reg}/Th17 Balance in the Gastrointestinal Tract—In nonhuman primate models of lentiviral infection, disease progression is associated with induction of T_{reg} and loss of Th17 cells; thus, the T_{reg} /Th17 balance is skewed towards T_{reg} [96, 109]. This development is strongly associated with increased systemic immune activation: Th17 are preserved in nonpathogenic SIV infection, but T_{reg} are expanded and Th17 lost in progressive SIV disease [96, 109, 110]. The enzyme indoleamine 2,3-dioxygenase (IDO) plays a critical role in regulating the T_{reg} /Th17 balance. Expressed by certain antigen-presenting dendritic cells, IDO is upregulated by interferons and TLR agonists, which may be triggered by numerous infectious and inflammatory conditions [111]. Increased IDO activity leads to higher levels of tryptophan catabolites, inducing Foxp3 expression and T_{reg} development, and suppressing the Th17 lineage [112]. This dysregulation contributes to the persistent inflammatory state observed in tissues during chronic HIV-1 disease [113, 114], which is only partially reversed by antiretroviral therapy (ART) [114]. Conversely, loss of $CD103^+$ mucosal dendritic cells (DC), a subset that can induce naïve T cells to express *RORc*, has been associated with loss of mucosal lymphocytes producing IL-17 and IL-22 in the SIVmac model [115]. Altered T-cell homing patterns also contribute to the Th17/T_{reg} imbalance: expression of chemokine CCL20 by small intestine epithelial cells is perturbed in chronic HIV-1 infection, including in ART-treated individuals. This leads to impaired homing of $CD4^+$ T cells expressing the chemokine receptor CCR6, specifically Th17 cells, to the small intestine, and the proportion of gut T_{reg} is correspondingly increased [116].

Intriguingly, administration of a lactobacillus probiotic along with IL-21 and ART during chronic SIV infection led to reduced IDO activity and expansion of intestinal Th17 cells, suggesting that such approaches might help restore mucosal immune homeostasis during chronic HIV-1 infection [117, 118].

3.3.4. Th22 Cells—The cytokine IL-22 promotes innate defense against mucosal pathogens, is important for maintaining mucosal barrier integrity, and promotes epithelial modeling and repair [119]. Although IL-22 is produced by Th17 cells, a distinct subset of $CD4^+$ T cells found in epithelia of the skin and GI tract produces IL-22 in the absence of IFNγ and IL-17; this subset has been designated Th22 [97, 120–122]. Th22 cells share certain common surface markers with Th17 cells (e.g., CCR4 and CCR6), but also express CCR10 and the aryl hydrocarbon receptor [97, 120–122]. Like Th17, Th22 cells also express CCR5 and are depleted during HIV-1 infection, and their loss is associated with a loss of epithelial barrier function and increased microbial translocation [123]. Evidence from *in vitro* studies and the SIVmac model revealed that the Th17 and Th22 subsets act cooperatively to maintain mucosal barrier functions [124]. Also, SIVmac-infected animals with high colorectal Th17 and Th22 numbers and function had significantly lower levels of SIV DNA, both during ART and after ART interruption, than animals with fewer and/or less functional Th17 and Th22 cells [125]. Thus, colorectal IL-17 and −22 producing $CD4^+$ T cells may be regulators and predictors of HIV/SIV viral persistence [125].

3.4. Gastrointestinal B Cells

Although B cells are quite abundant in mucosal tissues, few reports have addressed the effects of HIV-1 infection on mucosal B-cell populations. Hypergammaglobulinemia and

polyclonal B-cell activation were reported early in the HIV-1 epidemic [126, 127], and increased B-cell apoptosis has been detected in lymphoid tissues [128]. Histology has revealed loss of germinal center structure in lymph nodes during acute HIV-1 infection, a finding that was extended to germinal centers in terminal ileum Peyer's patches, with 88% of follicles exhibiting B- or T-cell apoptosis and follicular lysis [129].

There is a paucity of HIV-1-specific IgA production in plasma and mucosal secretions in response to HIV-1 and SIV infection [130–132]; the reasons for this are currently unclear [133]. One hypothesis relates to the ability of HIV-1 Nef to perturb B-cell signaling and block immunoglobulin class switching [134, 135]. The proposed mechanism involves the formation of actin-driven cellular conduits that allow Nef to move from infected macrophages and dendritic cells into uninfected germinal center B cells. Accumulation of Nef in germinal centers has been associated with reduced expression of activation-induced cytidine deaminase (AID), an enzyme required for class switching [135].

Plasmablasts are cycling ($Ki67^+$) B cells that secrete immunoglobulins; they represent approximately 1 to 3% of circulating B cells in healthy individuals and are less differentiated than the mature antibody-secreting cells known as plasma cells [136]. In healthy individuals, blood plasmablasts produce mainly IgA [137]. In HIV-1 infection, the number and percentage of circulating plasmablasts are elevated compared to controls, and the proportion that are IgA-secreting is reduced [136]. However, most of these circulating plasmablasts likely arise from polyclonal B-cell activation and are not HIV-1-specific, which may partially explain why the antibody response fails to control HIV [136].

The bias towards IgG-secreting plasma cells reported in HIV-1 disease is not unique to HIV-1 infection, but also reportedly occurs in other conditions, such as Crohn's disease and chronic granulomatous disease (CGD), that lead to mucosal inflammation [138]. When intestinal inflammation is present, IgG-secreting plasma cells express increased CXCR4 and decreased CCR10; and the frequency of $CXCR4^+/IgG^+$ plasma cells in the GI mucosa is associated with the severity of the inflammation [138]. These findings suggest that mucosal B cells may play an important role in mucosal immune cell homeostasis and the response to gut inflammation.

3.5. Beyond T and B Cells: Innate Effector Subsets

3.5.1. Natural Killer (NK) Cells—Although there have been extensive studies of NK cells in peripheral blood in the setting of HIV infection, few studies have focused on the role of mucosal NK cells. Mucosal NK cells are often characterized as belonging to the ILC1 group of innate lymphocytes [139], described in the section below. Mela and colleagues [140] reported depletion of NK subsets in the colonic lamina propria of viremic HIV^+ subjects, and partial reconstitution of these cells following ART in subjects with undetectable viremia. Taborda and colleagues [141] detected reduced expression of the activation marker CD69 on colonic NK cells in a cohort of Colombian HIV controllers compared to typical progressors. Sips and colleagues [142] identified two distinct populations of colonic $NKp46^+$ NK cells: the first and more abundant subset in both HIV^+ and HIV^- individuals was localized to the HIV- intraepithelial region; the second was localized to the lamina propria. There was a general trend towards decreased frequencies of

both subsets in untreated HIV^+ individuals with high viral HIV-/loads, as compared to HIV^- subjects. Intriguingly, HIV controllers expressing protective KIR/HLA genotypes showed a trend towards higher numbers of intraepithelial NK cells than controllers lacking protective genotypes, suggesting a possible role for these cells in immune control of HIV [142].

Despite species-specific differences, given the difficulties inherent in obtaining fresh mucosal tissue from human subjects, several groups have focused on elucidating mucosal NK cells in the SIVmac model system [143, 144]. Reeves and colleagues [145] demonstrated that chronic SIVmac infection induces expansion of blood NK cells expressing α4β7 integrin and lacking CCR7; these cells are presumably trafficking towards the gastrointestinal mucosa and away from lymph nodes. Two distinct NK subsets were described in SIV-infected macaques: $NKG2A^+$ NK cells, cytotoxic and IFNγ-producing, were distributed widely in blood and tissues; in contrast, $NKp44^+$ NK cells, non-cytotoxic and predominantly cytokine-producing (IL-22 and IL-17), were restricted to mucosal tissues [146]. Subsequent work led to re-classification of the $NKp44^+$ subset as ILC3 cells [147]. In chronic SIV infection, this $NKp44^+$ population (now designated ILC3) was depleted from mucosal tissues and/or adopted a modified functional profile, with increased IFNγ, reduced IL-17 production and increased cytotoxic potential [146, 148]. These functional alterations were correlated with increased mucosal expression of inflammatory mediators such as IDO [146]. ART increased the frequency of rectal $NKG2A^+$ NK and peripheral blood $CD16^+$ NK cells, but did not restore a normal frequency of rectal $NKp44^+$ cells [148].

NK cells expressing CXCR6 are recruited to the liver via the chemokine CXCL16. A recent study by Evans and colleagues [149] suggested that translocation of microbial products during chronic SIV infection leads to increased production of CXCL16 by liver myeloid dendritic cells (mDC). This, in turn, leads to recruitment of hypercytotoxic NK cells that contribute to local inflammation and liver damage.

3.5.2. Innate Lymphocytes (ILC)—Until recently, little was known of the relatively rare populations of mucosal ILCs and how they respond to infection. Within the past 5 years, several studies have elucidated the various subsets of ILCs and their distinct roles in tissue repair and host defense. Although they lack a T- cell receptor, ILCs share phenotypic and functional properties with classical, MHC-restricted T- cell subsets; this similarity is reflected in their nomenclature. ILCs have been grouped into three categories: ILC1, 2 and 3. Human ILC1 share many features with Th1 cells and/or tissue resident memory T cells [139, 150], such as production of IFNɣ in response to IL-12 and IL-15, intraepithelial location and evidence of TGFβ imprinting, and have been described by some as an innate counterpart of T_{RM} [151]. NK cells fall within the ILC1 designation [139]. ILC2, with properties similar to Th2 T cells, express transcription factor GATA-3 and secrete IL-5 and IL-13. ILC2 play important roles in the host response to helminthes, as well as in the pathogenesis of allergy and asthma [152, 153]. ILC3, analogous to Th17 cells, express RORγt, and secrete cytokines IL-17 and IL-22. ILC3 are important for the host response to extracellular bacteria and for regulation of microbiota [154]. Group 3 ILCs also encompass lymphoid tissue inducer cells (LTi), which are essential for the development of lymphoid tissues during embryogenesis, and continue to regulate lymphoid architecture after birth [155–158].

Despite certain functional similarities to $CD4^+$ T-cell subsets, ILCs do not express receptors for HIV/SIV and are not infectable by either virus [159]. Nevertheless, ILC3 are progressively depleted from the GI tract in SIVmac-infected rhesus macaques [147, 160, 161] and in humanized mice infected with HIV-1 [162]. ILC3 in rhesus macaques, identified as $CD3^-$/$NKp44^+$ and producing IL-17, undergo significant depletion in colonic and jejunal lamina propria during acute infection [147]. Apoptosis appears to be the primary mechanism driving depletion, as these cells increase their expression of activated caspase-3 by greater than 100-fold by 14 days post-infection [147]. Although $NKp44^+$ ILCs are normally noncytotoxic, under inflammatory conditions they can acquire cytotoxic potential [146]; during chronic SIV infection these cells reportedly increased intracellular perforin expression by 4-fold in colon, jejunum and mesenteric lymph nodes, modulating their phenotype towards that of the ILC1 subset [147].

Studying ILC dynamics in peripheral blood, Kløverpris and colleagues [163] demonstrated rapid loss of all ILC subsets during acute HIV-1 infection concomitant with an increase in plasma I-FABP, a marker of immune activation. This depletion appeared to be mediated by apoptotic pathways, a finding supported by *in vitro* studies showing that rhesus ILC3 could be induced to undergo apoptosis by microbial products signaling through the TLR2 and/or TLR4 pathways [160]. Blood ILCs could be preserved by initiation of ART during acute, but not chronic, HIV-1 infection [163]. Much work remains in order to fully elucidate the significance of ILC subsets, their role in intestinal homeostasis, and their capacity for plasticity, as well as clarification of differences in ILC dynamics between the SIVmac/rhesus macaque model and human HIV-1 infection.

3.5.3. NKT and Mucosa-associated Invariant T Cells (MAIT)—NKT and MAIT cells are T cells with limited receptor diversity that are considered to exhibit properties of both the innate and adaptive immune system: like adaptive immune cells (e.g., conventional T and B cells), they express antigen receptors generated through V(D)J recombination; however, like ILCs, they recognize a limited range of foreign antigens and respond quickly to challenge [164, 165]. NKT cells express certain receptors typical of NK cells, including CD161 in humans and NK1.1 in mice. In humans, most NKT cells express a T-cell receptor (TCR) that includes Vα24 co-expressed with Jα18 and Vβ11 [164]. Unlike conventional T cells, whose TCRs recognize short peptides presented by MHC class I or II, NKT cells recognize glycolipid antigens presented by the nonclassical MHC-like molecule CD1d. These glycolipids include the model antigen α-galactosylceramide (αGalCer); α-glycuronylceramides from the cell walls of certain Gram-negative, LPS-negative bacteria; and the mammalian glycosphingolipid isoglobotrihexosylceramide [164]. CD1d is expressed on antigen-presenting cells, including DC and B cells. Upon TCR stimulation, NKT cells respond rapidly by producing IFNγ and IL-4. A role for NKT cells has been suggested in a wide range of conditions including autoimmune diseases, allergy, atherosclerosis, and infectious diseases including bacterial, parasitic and viral infections [164]. Accordingly, while these cells do not directly respond to HIV-1 antigens, their loss and/or dysregulation in HIV-1 infection may have important consequences for the immune system.

NKT cells can be subdivided into $CD4^+$ and $CD4^-$ subsets with differential expression of tissue homing receptors; both subsets frequently express CXCR4 and CCR5 [166].

Peripheral $CD4^+$ NKT cells, particularly those expressing CD62L, are lost in viremic HIV-1 infection [166–168], but may be expanded upon treatment with IL-2 [169]. Reconstitution of blood NKT is delayed after effective ART [170], and those NKT cells that persist during chronic HIV infection display functional impairment and elevated expression of the exhaustion marker PD-1 [171]. In addition, the HIV-1 protein Vpu can interfere with dendritic cell-mediated presentation of lipid antigens to NKT cells [172]. In the GI tract, HIV infection leads to preferential loss of $CD4^+$ NKT cells, and the extent of NKT loss is related to the level of systemic immune activation [173].

Like NKT cells, human mucosa-associated invariant T cells (MAIT) express CD161 and a semi-invariant T-cell receptor, in this case usually encoded by Vα7.2 and Vβ2 or 13. The majority of human MAIT cells are CD8+, expressing either CD8αα or αβ, with minor populations of CD4+ or double negative MAITs [174]. MAIT cells are present at relatively high frequency in mucosal tissues, including the GI tract and liver, and recognize microbial vitamin metabolites presented by the nonclassical MHC-like molecule MR1 [175]. Upon stimulation, MAIT cells express both proinflammatory and tissue protective cytokines including IFNγ, TNFα, IL-17 and IL-22.

Although MAIT cells are predominantly $CD8^+$, rather than $CD4^+$, and therefore not directly infected by HIV, MAIT cells are significantly depleted from blood in viremic HIV-1 infection [174, 176–179], with an apparently slower decline in colorectal mucosa [174]. The functionality of remaining MAITs is reduced, with decreased cytokine production and cytotoxicity in response to bacterial antigen [180]; functionality is partially restored following suppressive ART, while MAIT numbers are not [174, 181]. While the underlying cause of MAIT cell loss in HIV-1 infection is not known, data suggest a mechanism driven by persistent exposure to microbial antigens, resulting in exhaustion and apoptosis [181]. There have been some discrepancies between reports in the kinetics of MAIT cell loss and subsequent repopulation on ART, likely due to differences in subject characteristics, mucosal sampling sites, and markers used to identify MAIT cells [174, 176, 182]. Studies in rhesus macaques revealed reduced MAIT cell frequencies in blood, mesenteric lymph nodes, and bronchoalveolar lavage of SIVmac-infected macaques compared to uninfected controls [183]. However, no significant differences between groups were detected in jejunum or liver, and increased expression of Ki67 in SIVmac-infected macaques suggested greater MAIT cell proliferation and turnover compared to uninfected macaques in this particular study [183]. Further work is needed to fully elucidate the role of MAIT cells in HIV/SIV infection, the mechanism(s) driving their loss and repopulation, and consequences of their loss or dysfunction for immune control of other microbes.

3.5.4. Gamma Delta T Cells—In humans, GI IELs are predominantly $CD8^+$, with the majority expressing the TCR α and β chains [184]. A minority of human intestinal IEL are γδ T cells, although this subset is far more abundant in mice [185, 186]. Nevertheless, γδ T cells, also present in other mucosal tissues and skin, play important roles in immune regulation, tumor surveillance, and innate immune responses to pathogens. They can recognize three sets of stimuli: TCR ligands, including microbial and endogenous phosphoantigens; stress-induced ligands that engage activating natural killer receptors (NKRs) such as NKG2D; and/or pathogen-associated molecular patterns (PAMPs) that are

recognized by pattern recognition receptors (PRR) such as Toll-like receptors and Dectin-1 [187]. TCR γδ cells can produce a wide range of cytokines, including those typically associated with Th1 (IFNγ), Th2 (IL-4, and IL-13), and Th17 (IL-17) subsets; they can also exhibit cytotoxicity mediated by FAS, TRAIL-R, and the perforin/granzyme pathway [187]. This broad range of functions can be explained by the existence of multiple TCR-γδ subsets, by developmental programming, and to some extent by functional plasticity. In human peripheral blood, the Vγ9Vδ2 (also referred to as Vγ2Vδ2 [188]) variable regions predominate; however, in the GI the dominant population expresses Vδ1 [187]. Vδ1 T cells recognize primarily MICA and MICB, which are stress-induced molecules expressed on intestinal epithelial cells [189]. In HIV infection, absolute numbers of TCR-γδ cells are increased, and activated Vδ1-expressing cells are expanded in blood and lungs, causing an inversion of the normal Vδ1/Vδ2 ratio in blood [190].

Investigating mucosal γδ in HIV-1 infected adults, Brandtzaeg, Nilssen and colleagues [185,191] reported that the γδ T-cell subset in duodenal mucosa was enriched in HIV^+ subjects compared to controls, both in percentage and absolute number per unit area. Most were negative for CD8 and >90% expressed the Vδ1/Jδ1 TCR segments. Their abundance in the HIV^+ group was inversely related to serum markers of immune activation such as neopterin and β2 microglobulin, and was lowest in individuals with advanced disease. Subsequently, Poles and colleagues [192] demonstrated expansion of Vδ1 and contraction of Vδ2 populations in both rectosigmoid mucosa and blood of HIV^+ individuals; these changes were detected during acute infection, persisted into the chronic phase, and were not reversed by HAART. Although the mechanisms driving these changes are not entirely clear, and most γδ T cells do not express CD4, Vγ2Vδ2 T cells that express CCR5 and α4β7 integrin can reportedly be induced to undergo caspase-mediated cell death following binding to soluble or cell-associated gp120 from CCR5-tropic HIV [188].

In a nonhuman primate model of nonprogressive lentiviral disease, sooty mangabey monkeys infected with SIVmac did not develop the inversion of the normal Vδ1/Vδ2 ratio that is typically observed in blood of HIV^+ individuals [193]. In contrast, rhesus macaques infected with pathogenic SIVsmE543 did exhibit SIV-associated inversion of the Vδ1/Vδ2 ratio in blood and tissues, corresponding to expansion of the Vδ1 subset. Macaque γδ T cells were not infected by SIV *in vivo,* and the stimulus responsible for Vδ1 expansion appeared to be microbial translocation [194]. Intriguingly, peripheral Vγ9Vδ2 T cells were recently reported as a previously unrecognized reservoir of latent HIV infection [195]. The proposed mechanism involves upregulation of CD4 and CCR5 due to pathological immune activation in early HIV infection [195].

4. CONCLUSIONS AND FUTURE DIRECTIONS

Mucosal tissues play a major role in the transmission and pathogenesis of HIV infection, and these tissues house a variety of novel immune cell subsets that are phenotypically and functionally distinct from their counterparts in peripheral blood. While the challenges inherent in tissue sampling have prevented full exploration of mucosal tissues in the past, new technologies in imaging, gene and protein expression analysis and bioinformatics, are now poised to elucidate these novel cell subsets and their interactions in exciting new ways.

New approaches for measuring viral persistence *in situ* will enhance our understanding of host-virus interactions in tissues. Much work remains in order to fully understand the nature of innate and adaptive immunity in tissues, the trafficking patterns of mucosal immune cells, the concept of 'tissue residency', and the plasticity of immune cell subsets. Perhaps the greatest challenge remains that of utilizing this information to develop novel preventive and therapeutic strategies that will ultimately lead to eradication of HIV/AIDS.

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List of Abbreviations

SAMHD1	Sterile alpha motif domain and histidine-aspartic domain-containing protein 1
SLPI	Secretory leukocyte protease inhibitor
HBD2	Human beta-defensin 2
MICA, MICB	MHC class I polypeptide-related sequences A and B

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