Title

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Journal

Current immunology reviews, 15(1)

ISSN

1573-3955

Authors

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Publication Date

2019

DOI

10.2174/1573395514666180807113928

Peer reviewed

HHS Public Access

Author manuscript

Curr Immunol Rev. Author manuscript; available in PMC 2020 January 01.

Published in final edited form as:

Curr Immunol Rev. 2019 ; 15(1): 36–40. doi:10.2174/1573395514666180807113928.

T Cells in the Female Reproductive Tract Can Both Block and Facilitate HIV Transmission

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Abstract

Because HIV is sexually transmitted, there is considerable interest in defining the nature of anti-HIV immunity in the female reproductive tract (FRT) and in developing ways to elicit antiviral immunity in the FRT through vaccination. Although it is assumed that the mucosal immune system of the FRT is of central importance for protection against sexually transmitted diseases, including HIV, this arm of the immune system has only recently been studied. Here we provide a brief review of the role of T cells in the FRT in blocking and facilitating HIV transmission.

Keywords

vagina; cervix; T cell; HIV; sexually transmitted disease

1. INTRODUCTION: The Role of T Cells in Viral Infections, Especially HIV.

Mammals have evolved an elegant immune system to cope with infectious organisms. The adaptive arm of the immune response, consisting of antibodies and T cells, is critical for limiting and clearing viral infections. The humoral immune response consists of antibodies specific for the virus that can capture and neutralize virus particles before they enter the cell and kill virus-infected cells through antibody-dependent cellular cytotoxicity. However, most virus-infected cells can only be cleared by the cellular arm of the adaptive immune system. After infection, the virus uses the protein-synthesis machinery of the host cell to synthesize its own proteins. During this process, some of the newly synthesized viral proteins are degraded into peptide fragments and, if they have sufficient affinity, bind to MHC class I molecules. These MHC class I-peptide complexes will then be presented on the surface of the infected cell. Activated CD8+ T cells specific for the viral peptide, recognize the MHC class I-peptide complex and induce apoptosis of the infected cell by releasing cytotoxic granules (1). In contrast, CD4+ T cells may be activated by antigens presented by antigen-

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presenting cells (APC) or cells expressing MHC class II antigens, yet the mechanisms of these pathways are only now being examined in detail.

Memory T cells provide rapid and highly effective protective immunity against previously encountered pathogens, and can recognize a wide variety of viral antigens. Lymphocytic choriomeningitis virus (LCMV) infection of mice is used as a model to study the role of CD8+ and CD4+ T cells in both acute and chronic viral infections. When mice, deficient in either CD8+ or CD4+ T cells, are inoculated with LCMV, they cannot clear the virus and develop persistent infections (2). Thus, in this viral infection of mice, both CD8+ and CD4+ T cells are required to clear the virus. In humans, both CD8+ and CD4+ T cells play a central role in protection from diseases caused by measles virus, cytomegalovirus (CMV), hepatitis C virus (HCV), and HIV (3–6). In addition, after human infection with pandemic H1N1 influenza virus, the number of pre-existing CD8+ T cells specific for conserved viral epitopes, was associated with disease severity (7). CD8+ T cells can also mediate protection from influenza virus challenge. In healthy volunteers challenged with influenza A virus, pre-existing cytotoxic CD4+ T cells responding to influenza virus internal proteins were associated with less severe illness and decreased virus shedding (8). Thus, both CD8+ and CD4+ T cells are important immune effector cells in the protective human immune response against the influenza virus. In general, both CD4+ and CD8+ T cells are required to successfully combat viral infections likely through antigen-specific, cooperative mechanisms.

In HIV infection, CD4+ T-cell responses have been associated with partial protection as virus-specific cytolytic CD4+ T cells with unique transcriptional profiles have been shown to predict disease outcome in HIV patients (9). However, less is known regarding the precise role(s) that virus specific CD4+ T cells play in control or protection from HIV infection. Cytotoxic CD8+ T-cell responses have been examined in the FRT of macaques and humans in a number of studies. In chronic HIV infection, the host does not clear the virus but in most people antiviral cytotoxic T cells blunt virus replication to limit disease severity and delay disease progression. In fact soon after HIV infection, viral replication and HIV RNA levels in plasma decline due to the development of anti-viral T-cell responses (10). Individuals with the highest number of HIV-specific cytotoxic CD8+ T cells have lower plasma viral loads than patients with fewer HIV-specific cytotoxic T cells, indicating that cytotoxic CD8+ T cells can partially control virus replication (11). The critical role of CD8+ T cells was confirmed by studies documenting that loss of CD8+ T cells is associated with HIV disease progression (12, 13) and studies showing that HIV escape mutations often occur at HLA-binding sites specific for CD8 epitopes. The strong association of certain HLA-alleles with protection from HIV disease progression, the temporal relationship between viral load decline and increase in HIV-specific CD8+ T cells, and the results of CD8+ T cell depletion studies in non-human primate (NHP) models, underline the importance of CD8+ T cell responses in controlling progression to AIDS (3, 14–16). However, patients who control HIV replication also have an increased number of HIV-specific CD4+ T cells, suggesting that cytotoxic anti-HIV CD4+ T-cell responses can contribute to slowing the progression of HIV disease (9, 17).

1.2 Anatomic and Phenotypic Distribution of T Cells in the FRT

As detailed in an excellent review (18), until recently, memory T cells were divided into two major subsets: central memory T (TCM) cells and effector memory T (TEM) cells (19). TCM cells express the chemokine receptor CCR7 and the vascular addressing L selectin (CD62L), which enable them to access and enter lymph nodes from blood. TEM cells express little CCR7 and CD62L but have receptors that allow them to access peripheral tissues (for example, the E-selectin ligand Cutaneous Lymphocyte Antigen (CLA) for skin homing (20), α4β7 for gut homing (21) and CCR5 and CD11c for homing to the human FRT (22). Over the past decade, it has become clear that there is a third important subset of memory T cells: tissue-resident memory T cells, or TRM cells (18). TRM cells are found in epithelial barrier tissues at the interface between the host and the environment, such as the gastrointestinal (GI) tract, respiratory tract, reproductive tract and skin (23). TRM cells can respond rapidly to pathogen challenge at these sites prior to recruitment of T cells from the blood. They thus mediate the rapid protective immunity that is the defining feature of adaptive immune memory. The TRM cells in each barrier tissue are enriched for the specific pathogens that have been encountered previously through that barrier epithelium. Thus, the specificity of skin TRM cells is largely different from that of lung TRM cells, and the pathogen specificity of both skin and lung TRM are different from that of gut TRM cells. TRM are identified as CD69+ (24) and/or CD103+ T cells which are abundant in mucosal tissues (25). Finally, TRM cells have a gene expression pattern that is distinct from peripheral blood TEM cells and TCM cells (25), further indicating that they are a unique population of cells.

It is widely believed that primary immune T-cell induction in FRT occurs only in the draining lymph nodes (DLNs) but not in the mucosa itself due to a lack of mucosa-associated lymphoid tissue (MALT) or secondary lymphoid tissues (26, 27). Thus naïve T cells in lymph nodes draining the genital tract are primed by the antigen-bearing dendritic cells (DCs) migrating from the antigen-exposed mucosa and differentiate into memory T cells that are then able to traffic back to mucosal sites through the bloodstream (28–31). However, recent studies suggest that there can be local induction of immunity in the FRT and that local secondary immune responses can protect against viral infection (23, 25, 32). Further, protective vaginal immunity develops in lymph node-deficient mice (33) and lymphoid follicles can form in virus-infected vaginal mucosa (34). It was recently shown that primary induction of CD8+ T-cell responses in the type-II mucosa of the vagina, occurs locally without the help of draining LNs, MALT or any other tissue site of priming (35). Thus primary immune responses to viral infections may be induced in the FRT, and as detailed above, the FRT is rich in antiviral effector TRM T cells.

1.3 Role of FRT CD4+ T Cells in HIV Transmission

Most women acquire HIV through receptive vaginal sex. Exposure to seminal fluid and to various pathogens, including HIV, can cause mucosal inflammation that increases the number of activated CD4+ T cell targets for HIV and promotes local viral replication (36–38). In mice, chlamydia infection has been shown to increase the number of antigen-specific α4β7+ T cells migrating through the female genital tract and into gut-associated lymphoid

tissues (GALT) (39–43). In addition, HIV-infected women express higher levels immune activation markers on T cells in the ectocervix, compared to uninfected women (44). The CD4+ T cells recruited to the FRT by inflammatory conditions express the GALT integrin α4β7 and the HIV coreceptor CCR5. In cytobrush samples and blood collected from female sex workers (FSW) in Nairobi, Kenya the integrin α4β7 was expressed on 26.0% of cervical CD4+ T cells, and these cells usually expressed the HIV coreceptor CCR5 (45). Th17 cell frequency was higher in the cervix than in blood and cervical IL-17A+ CD4+ T cells preferentially coexpressed α4β7 and CCR5 (45). Consistent with the hypothesis that these cells are preferential HIV targets, cervical Th17 cells were almost completely depleted in HIV+ FSWs compared with HIV- FSWs (45). In addition, studies using single round reporter viruses in NHP models indicate that Th17 cells are the first cells infected in the vagina after SIV or SHIV vaginal challenge (46). Finally, a recent study characterized the phenotype and HIV susceptibility of CD4+ T cell in the human endometrium, endocervix and ectocervix of the FRT (47) reporting that CCR5+ Th17 cells represent a major T cell subset in the human FRT and that Th17 cells were highly susceptible to HIV-infection. In addition, the susceptibility of CD4+ T cells to HIV infection was lowest in the endometrial T cells and highest in ectocervical T cells (47).

Both α4β7 and CCR5 are competent HIV co-receptors for infecting CD4+ T cells *in vitro*, however the consistent co-expression of CCR5 and α4β7 on CD4+ T cells in the FRT makes it difficult to determine if one or both of these molecules are important co-receptors for virus transmission. Since vaginal SIV transmission can be blunted by systemic infusion of an anti-α4β7 monoclonal antibody (48) or topical vaginal applications of CCR5 fusion inhibitors (49, 50) these molecules must play some role in transmission. As most CCR5+ T cells are also α4β7 (45), the results could be due to blocking virion interaction with α4β7 acting as a co-receptor, perturbing α4β7/CC5+ T-cell physiology or limiting access to target cells. In fact, administration of recombinant rhesus α4β7 antibody results in significant transient decline of α4β7+ lymphocytes in both the periphery and GI tissues (51). Although the effects of recombinant rhesus α4β7 antibody administration on CCR5+ T cells were not reported, it is likely that they were also depleted given the fact that essentially all CCR5+ cells are also α4β7+ (45, 52). In fact, studies in SIV-infected macaques suggest that the rate of α4β7+CD4+ T-cell depletion exceeds that of CCR5+ cells, suggesting a greater affinity for, or role for α4β7 in viral pathogenesis (53). However, experimentally blocking of α4β7 with an orally available synthetic anti-α4 small molecule that blocks MAdCAM-1 and binds HIV-gp120 binding *in vitro*, did not protect macaques from SHIV acquisition after vaginal inoculation (54). Thus, the role of α4β7 as an important HIV co-receptor involved in transmission remains difficult to demonstrate experimentally. It may be possible to clarify the role of these co-receptors by characterizing and comparing the founder viruses isolated from individuals with and without genital inflammation. Thus, founder viruses from women with genital tract inflammation would be expected to have HIV founder viruses that preferentially use α4β7 as a co-receptor. Founder viruses from women that acquire HIV despite little inflammation in the FRT would not preferentially use the α4β7 integrin as a co-receptor. However, the vaginal environment is dynamic, and it is difficult to sample women close to the time of actual HIV transmission, so NHP studies are necessary for understanding the earliest events in vaginal HIV transmission (55, 56).

1.4 Role of FRT CD8+ T Cells in Blocking HIV Transmission.

As CD8+ T cells are the dominant lymphocyte in the normal and inflamed FRT, most HIV studies have focused on virus-specific vaginal CD8+ T-cell responses. The first study to document antiviral CTL responses in the FRT, found SIV-specific CTL activity in CD8+ T cells from the vagina of experimentally infected female rhesus macaques (57). SIV p55gag and/or gp160env-specific lysis was detected in cultures of vaginal epithelial, but not submucosal, CD8+ T cells. The estimated SIV-specific precursor CTL frequencies were higher in the vaginal CD8+ intraepithelial lymphocyte population of chronically infected monkeys than in the same cells from acutely infected or naive control monkeys. These results provided the first demonstration that antiviral CTL are present in the vaginal epithelium. Subsequently, Musey et al. (58) demonstrated that HIV-1-specific CTL (involving both CD4 and CD8 cells) could be generated from cervical specimens in HIV-1-infected women. In these HIV-1-infected women, comparisons of intra-individual cervical and blood CTL specificities also indicated that epitopes recognized by CTL in the cervix were commonly recognized in the blood, although relative frequencies of CTL in cervix and blood were not examined (58). In most cases, the frequency of the antiviral CD8+ T cells in the cervicovaginal compartment exceeds the frequency of the antiviral CD8+ T cells in the blood or the draining iliac lymph node. In one study, the percentage of Gag-tetramer-positive CD8+ T cells were as high as 13 to 14% of the CD3+ CD8+ T-cell population in the vaginal and cervix of SIV and SHIV chronically infected macaques (59). Another macaque study confirmed these results, finding that the frequency of SIV Gag tetramer-specific CD8+ T cells was 3-to 30-fold higher in FRT tissues than in peripheral blood of chronically SIV-infected macaques (60). Further, the SIV-specific CD8+ T cells in FRT expressed high levels of CXCR3 and CCR5, chemokine receptors normally expressed on memory T cells that home to inflamed tissues. Thus, in chronic infection the frequency of SIV-specific CD8+ T cells in the FRT is enriched compared with peripheral blood, and these T cells are recruited to the FRT by local inflammation (60).

It has also been demonstrated that there are CD8+ T cell IFNγ responses to HIV-1 CTL peptide epitopes in the cervix of some highly exposed, uninfected Kenyan sex workers. As in chronically infected women, the specificity of these HIV responses was similar to systemic (PBMC) responses. However, HIV-1-specific responses were enhanced in the genital tract compared to the blood, and persisted in some subjects for up to 5 months (61). Although HIV/SIV-specific T cells are present in the FRT of chronically infected women and macaques as described above, they are thought to be largely mono-functional and, thereby, may have limited functional antiviral capacity (62–64).

After vaginal SIV inoculation, robust anti-SIV CTL responses are present in the FRT a few days after the peak plasma vRNA is reached but after the virus has disseminated widely to all lymphoid tissues (65, 66). In contrast, the CD8+ T cell responses are still modest in the draining genital and peripheral lymph nodes at the same time. Thus, after vaginal transmission virus-specific CD8+ T-lymphocyte responses in the FRT are relatively rapid but they cannot prevent virus dissemination (65, 66). However, we found that CD8+ T-cell responses induced by an attenuated lentivirus infection prior to vaginal challenge with pathogenic SIV protect some rhesus macaques from infection and prevented uncontrolled

viral replication and virus dissemination in the majority of animals that became infected (67–69). Further, CD8+ T cells in the FRT mediated this protection (68, 69). Thus, immunization with a chimeric simian/human immunodeficiency virus (SHIV) results in a systemic infection that induces a moderate population of SIV-specific CD8+ and CD4+ T cells with cytolytic potential in the vaginal mucosa (69). Depletion of CD8+ T cells at the time of SIV challenge completely abrogates the protection mediated by prior infection with attenuated SHIV. Further, after vaginal SIV challenge, the only significant expansion of SIV-specific T cells occurs in the vagina in these animals, without expansion of T-cell responses in systemic lymphoid tissues (68).

1.5 CONCLUSION

Although the natural CD8+ T-cell response to virus infection does not eliminate infection, the fact that some highly exposed, uninfected Kenyan sex workers have cervical anti-HIV CD8+ T-cell responses suggests that pre-existing effector T-cell responses in the FRT may be beneficial in resisting HIV transmission. Further, the presence of SIV-specific CD8+ T cells in the vagina on the day of vaginal SIV challenge and a modest expansion of local effector T cells is sufficient to prevent uncontrolled SIV replication. It seems that T-cell-based vaccine strategies that can elicit mucosal effector CD8+ T-cell populations and avoid inducing systemic T-cell proliferation/activation upon exposure to HIV have the greatest potential for mimicking the success of live-attenuated lentiviral vaccines. On the other hand, the role of cervico-vaginal CD4+ T cells, innate responses, the vaginal microbiome and responses to hormonal fluctuations may also play a role in susceptibility or resistance to HIV infection. More studies are still needed to optimally induce effective antibody and cellular responses in the FRT to protect against HIV transmission.

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