INTRODUCTION

Cell-Associated HIV Mucosal Transmission: The Neglected Pathway

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This supplement to *The Journal of Infectious Diseases* is devoted to the important and understudied topic of cell-associated human immunodeficiency virus Type 1 (HIV) mucosal transmission. It stems from a workshop held in Boston, Massachusetts, in October 2013, in which scientists discussed their research and insights regarding cell-associated HIV mucosal transmission. The 10 articles in this supplement present the case for cell-associated HIV transmission as an important element contributing to the HIV epidemic, review evidence for the efficacy of current HIV prevention strategies against cell-associated HIV transmission and opportunities for further development, and describe in vitro, ex vivo, and animal cell-associated transmission models that can be used to further elucidate the molecular mechanisms of cell-associated HIV mucosal transmission and test HIV prevention strategies. We hope that these articles will help to inform and invigorate the HIV prevention field and contribute to the development of more-effective vaccine, treatment, and microbicide strategies for HIV prevention.

Keywords. HIV; cell-associated; transmission; mucosa; vagina; semen; breast milk.

Many enveloped viruses, including human immunodeficiency virus type 1 (HIV), are efficiently spread from cell to cell without appearing as free virions, a mechanism called cell-associated transmission. Cell-associated HIV transmission is more efficient than cell-free HIV transmission because of concentrated production of virus at intercellular contact points, directional secretion through specialized intercellular synapses, and, possibly, decreased vulnerability of virus to host restriction factors and antiviral factors in the environment during transmission. Genital secretions and breast milk from HIV-infected individuals can contain HIV-bearing cells that are viable and infectious; it is plausible that these cells play an important role in the mucosal transmission of HIV. However, cell-associated HIV transmission has been largely overlooked in studies of the mechanisms of HIV transmission and in the design and testing of HIV vaccine and microbicide candidates. Current preclinical assays for the development of HIV prevention drugs and vaccines predominately use cell-free viral stocks. Since the molecular events underlying cell-associated HIV transmission differ from those involved in cell-free transmission, many of the current vaccine and microbicide candidates shown to be effective against cell-free virus may not protect against cell-associated HIV transmission. The failure of several recent vaccine and microbicide clinical trials to prevent HIV transmission may be due, in part, to this oversight.

The goal of this supplement is to review current data supporting cell-associated HIV mucosal transmission; to describe in vitro, ex vivo, and animal models that can be used to test HIV prevention strategies for efficacy against cell-associated HIV transmission; and to speculate on the application of this knowledge to the development of more effective HIV prevention strategies.

In this supplement, Politch et al [1] review evidence for the presence and characteristics of HIV-infected cells in genital secretions. Semen and cervicovaginal secretions contain variable numbers of CD4+ T cells and macrophages, the numbers of which can be

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dramatically elevated under conditions of infection and/or inflammation. Macrophages are the predominant HIV host cell in genital secretions; the proportion of CD4+ T cells decreases with HIV infection, as it does in blood. The phenotypes of mucosal immune cells differ from those in peripheral blood: most T cells in genital secretions express α4β7 (mucosal phenotype), CD45RO (memory phenotype), and high levels of CCR5 and CXCR4 (HIV coreceptors). Mucosal macrophages generally express the tissue (M2) phenotype. Isolated mononuclear cells from genital secretions of HIV-infected men and women often contain HIV provirus, indicating the presence of HIV-infected cells, and lymphocytes and macrophages isolated from semen of HIV-infected men are viable and highly infectious in vitro. This evidence strongly supports the presence of HIV-infected cells in genital secretions that are capable of cell-associated HIV transmission.

Cone [2] reviews factors in the female genital tract that may affect cell-associated HIV transmission. Foremost are endogenous vaginal microflora. Lactobacilli, which dominate in most healthy reproductive-aged women, create an acidic environment that is inhospitable to both cell-free and cell-associated HIV. The diverse bacterial species that constitute bacterial vaginosis promote a proinflammatory neutral pH environment, which has been associated with HIV susceptibility. Cone speculates that cell-associated transmission is favored when the vagina is not acidified (ie, during the prepuberty and postmenopause periods and during bacterial vaginosis).

Houzet et al [3] review the origins of infected leukocytes in semen and the compartmentalization of HIV in the male genital tract that gives rise to distinctive HIV signatures in seminal leukocytes. HIV-infected cells in semen likely originate from several sites in the male genital tract: the epididymis, accessory glands (seminal vesicles and prostate), and urethra. These sites can shield HIV from immunologic and pharmacologic pressure, and distinctive HIV sequences have been described in semen. HIV-infected cells, as well as free virions, persist in semen of men who are receiving antiretroviral therapy and have undetectable HIV in blood; this provides evidence that cell-associated transmission may occur despite suppressive antiretroviral therapy.

Milligan and Overbaugh [4] review evidence for cell-associated HIV infection in mother to-child transmission. Three periods are covered: transplacental infection during gestation (5%–10% of infections), peripartum infection during labor (33%–50% of infections), and postpartum infection via breast-feeding (up to 40% of infections). Evidence supporting cell-associated HIV transplacental infection is provided by in vitro experiments showing cell-associated HIV (but not cell-free HIV) transcytosis across polarized trophoblast monolayers. Several studies have shown a significant correlation between levels of genital tract HIV DNA and risk of intrapartum transmission. Finally, HIV-infected cells have been described in breast milk, and in vitro studies have shown that these cells are capable of crossing the intestinal epithelium in newborns.

Gummuluru [5] reviews evidence for the role of mucosal dendritic cells in cell-associated HIV transmission and in facilitating the systemic distribution of HIV. CD169 Is identified as a dendritic cell–associated HIV attachment factor and attractive target for intervention of cell-associated HIV transmission.

Anderson [6] reviews in vitro assays used to assess and characterize cell-associated HIV mucosal transmission. Electron and fluorescence microscopy were first used to characterize the molecules and synapse structures involved in cell-associated HIV transmission. Currently, coculture and explant infection assays are used to assess cell-associated HIV transmission. Although these assays provide a valuable adjunct for microbicide and vaccine-associated antibody screening, they need further refinement to authentically represent mucosal HIV transmission.

Moench [7] discusses small-animal models of cell-associated HIV transmission. Feline immunodeficiency virus (FIV) is transmitted sexually via infected cells and free virus. It was used as an early model for tests of microbicide efficacy against cell-associated challenge. Interestingly, a vaccine is now available to prevent FIV infection. Another small-animal model for studies of cell-associated HIV transmission is the humanized mouse. HIV-infected cells transmit infection via rectal and vaginal routes; this model shows considerable promise for use as a screening tool for microbicide and vaccine candidates.

Bernard-Stoecklin et al [8] review nonhuman primate models for cell-associated HIV transmission. Semen from simian immunodeficiency virus (SIV)–infected macaques contains SIV-infected T cells and macrophages, similar to the situation with HIV in humans. Several groups have now shown that SIV-infected leukocytes are capable of transmitting infection when placed in the macaque vagina and that the infectious dose is much lower than that required for cell-free infection. This provides valuable evidence that cell-associated HIV transmission occurs in humans and supports the use of nonhuman primate model systems for testing microbicide and vaccine efficacy against cell-associated HIV transmission.

Sagar [9] reviews evidence for cell-associated HIV transmission in humans. Studies comparing cell-associated and cell-free HIV sequences from the infecting partner to those present in a newly infected recipient have been inconclusive. Nonetheless, evidence that transmitted strains have ancestral properties and that a limited number of viruses breech the epithelium could suggest that infected cells are often the source of infection.

The final article, by Whaley and Mayer [10], reviews evidence for the efficacy of current antiviral, vaccine, and microbicide regimens in preventing cell-associated HIV transmission. They emphasize that more data and model systems are needed in this field to guide HIV prevention strategies.

Collectively these reports point to critical blind spots in our understanding of mucosal transmission of HIV and suggest some of the next areas that need to be addressed in future research. The relative importance of CA-HIV transmission continues to be debated as evidence mounts for the biological plausibility of this mechanism. We hope that the reviews included here from our workshop will help advance efforts to prevent the transmission of HIV and further curb the ongoing AIDS epidemic.

Notes

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