

Insights into the Local HSV-2 T-Cell Response in the Female Genital Tract

August 18, 2014

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Infection with herpes simplex virus 2 (HSV-2) is a primary cause of genital lesions. This viral infection is highly prevalent worldwide, affecting 17% of American adults and as high as 95% in some populations, such as HIV-positive individuals and female sex workers. Aside from causing genital lesions, HSV-2 infection also increases a person's susceptibility to HIV infection. Much effort has been dedicated to elucidating details of the local innate and adaptive immune responses to HSV-2 infection and reactivation. Human studies have predominantly involved characterizing the T-cell responses to HSV-2 in the blood, skin and eye. The characteristics of the T-cell repertoire at the site of infection and reactivation were recently reported by researchers from the Vaccine and Infectious Disease Division in the journal *Mucosal Immunology*. A detailed analysis of the local T-cell response to HSV-2 infection in the female genital tract was possible by obtaining cells from the cervixes of HSV-2-positive females.

"The need for a vaccine for HSV-2 is great," said lead author of the study Dr. Christine Posavad, "and we believe the knowledge gained in uncovering mechanisms of T-cell protection in the female reproductive tract will inform the design of prophylactic vaccines and novel immunotherapies directed at HSV-2." Indeed, the development of any therapeutic intervention directed at treating or preventing HSV-2 infection will likely rely heavily on data about the local immune responses to the virus observed at the site of infection and reactivation.

The researchers obtained cervical cytobrush samples from HSV-2-infected and seronegative control subjects. T cells from these samples were expanded *in vitro* in order to test the cell phenotype and the ability of the cells to recognize HSV-2 antigens. Thirty HSV-2-infected patients provided at least two cervical cytobrush samples. A fairly high proportion of these samples (65%) contained T cells that proliferated in response to HSV-2 in lymphoproliferative assays.

Next, the researchers looked at the T-cell phenotype in the expanded T-cell populations. Of the CD3⁺ T cells obtained from the cervix that were specific for HSV-2, 91.3% of them on average were CD4⁺ T helper cells, while a median of 3.9% were CD8⁺ cytotoxic T cells. It is possible that discrepancies between the tendencies of the different cell types to expand after sample collection could have played a minor role in this finding. However, importantly the CD4⁺ T cells had a greater breadth of antigenic recognition of HSV-2 peptides. By looking at the phenotype of T cells that reactivated following incubation with pools of HSV-2 peptides, the researchers were able to compare the CD4⁺ and CD8⁺ cell subsets. The CD4⁺ T cells were found to recognize substantially more HSV-2 peptides than the CD8⁺ T cells (see figure). Thus, the CD4⁺ T cells not only made up a larger proportion of the CD3⁺ cervical T-cell population, but also displayed a greater breadth of antigenic recognition of HSV-2 than the CD8⁺ T cells.

Dr. Posavad explained, "Our data suggest that T-cell responses to HSV-2 are common and resident at mucosal sites of HSV-2 exposure and reactivation." Future studies will focus on the specific roles played by these T-cell populations during infection and reactivation of HSV-2, to inform potential vaccination strategies to prevent HSV-2 acquisition. "Our goal is to understand the mechanism of local containment of HSV-2 and to determine how resident memory T cells are established and maintained in the female reproductive tract," said Dr. Posavad, "To achieve this goal, we will need to analyze T-cell responses *ex vivo*, and we are currently optimizing these procedures in the lab."

[Posavad CM, Zhao L, Mueller DE, Stevens CE, Huang ML, Wald A, Corey L](#). 2014. Persistence of mucosal T-cell responses to herpes simplex virus type 2 in the female genital tract. *Mucosal immunology*. doi: 10.1038/mi.2014.47. [Epub ahead of print].

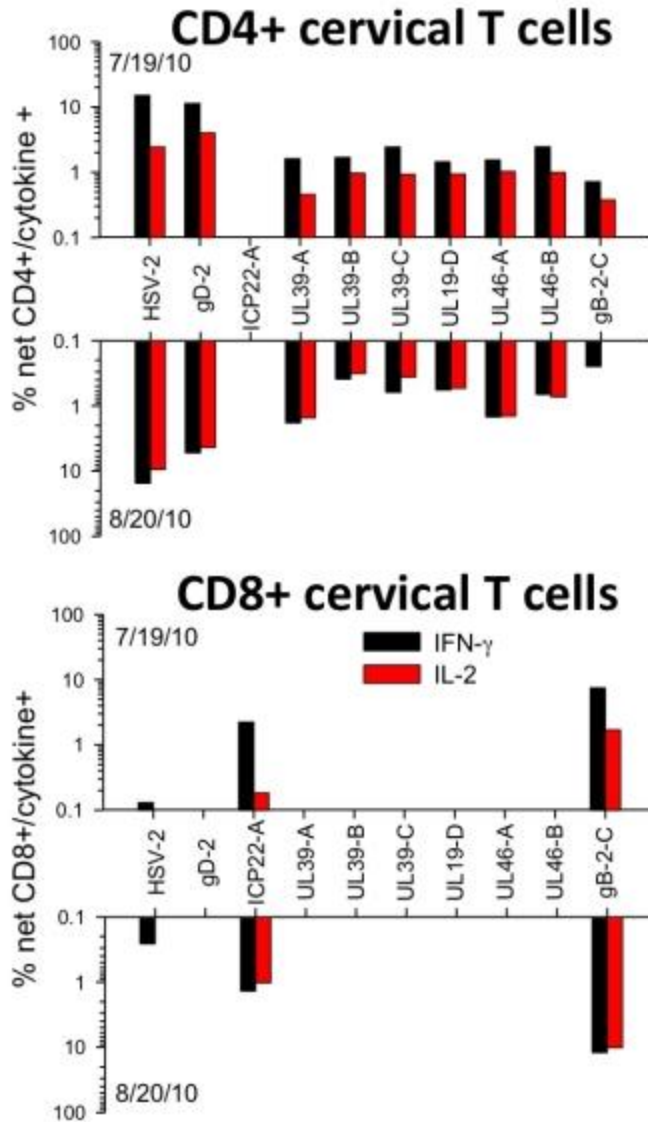


Image provided by Dr. Christine Posavad.

T cells expanded from cervical cytobrush samples obtained one month apart from an HSV-2-infected patient were assayed for antigenic recognition of HSV-2 and pools of HSV-2 peptides. The CD4+ T cell subsets (above), in addition to comprising a much larger proportion of the CD3+ T cell population, exhibited a much larger breadth of HSV-2 recognition than the CD8+ T cells (below). CD4+ and CD8+ T cells directed at the same HSV-2 peptide could be detected in the cervix over the one-month study period suggesting that they are resident and persist in the female genital tract.