HIV efficiently infects genital CD4+ T cells and remodels them to promote systemic viral spread

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Background
The female reproductive tract is one of the most common sites of initial HIV transmission yet we lack a detailed understanding of which cells at this portal of entry are most susceptible to infection. One challenge in classifying HIV-infected T cells is their extensive remodeling by HIV, making difficult to classify these cells into traditional T cell subsets. We took advantage of high-dimensional analytical methods to predict the original states of genital T cells prior to their remodeling by HIV.

Methods
We exposed paired specimens of endometrial biopsies and PBMCs from HIV seronegative donors to a CCR5-tropic transmitted/founder HIV-1 reporter virus, and then conducted an extensive phenotypic analysis of uninfected and infected cells using CyTOF. Using bioinformatics analyses of the resultant high-dimensional single-cell datasets, we characterized the subsets of cells that were most susceptible to HIV infection, and assessed which antigens were modulated as a result of infection.

Most subsets of Tm in endometrium but not blood are susceptible to HIV infection

Memory CD4+ T cells (Tm) are the dominant population of T cells targeted for infection

Memory CD4+ T cells were almost exclusively targeted for infection in both the tissue and blood specimens, but those from the endometrium were significantly more susceptible than those from blood (p<0.01). While a diverse array of endometrial memory CD4+ T cells were targeted for infection, only a small subset of PBMC-derived CD4+ T cells could be infected. In-depth analyses of the features of the endometrial memory CD4+ cells targeted for infection revealed preferential infection of T effector memory (Tem) cells polarized towards the Th1 and Th2 lineages, as well as preferential infection of T resident memory (Trm) and T follicular helper (Tfh) cells.

HIV preferentially infects endometrial Tem and Trm with phenotypic features of Th1, Th2, and Tfh cells

HIV remodels cells in ways that may impair TCR signaling and promote migration of infected cells to lymph node follicles

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Conclusions
Unique phenotypic features of memory CD4+ T cells in the genital tract render these cells highly susceptible to infection by HIV-1, and upon infection the virus remodels the cell in a manner that undermines TCR signaling while promoting survival and enhancing migration to other lymphoid sites via modulation of homing receptor expression.

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