

The Inner Foreskin Harbors a Pro-Inflammatory Environment

November 17, 2014

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Multiple clinical trials have proved the efficacy of circumcision in protecting from HIV-1 infection. However, the mechanisms explaining this finding have yet to be understood. Possible reasons include a decreased number of HIV target cells, or the reduction of the surface area susceptible to HIV-1 infection. A better understanding of the factors that prevent HIV-1 infection remains of vital importance to improve prevention strategies.

Dr. Maria Lemos from the Vaccine and Infectious Disease Division (VIDD) at Fred Hutch, in collaboration with two research institutions in Lima, Peru, conducted the clinical trial HVTN914 in order to clarify the differences between inner and outer foreskin, and to identify the mechanisms underlying protection by circumcision. For the study, foreskin samples were obtained from 20 HIV-1-exposed but uninfected men who have sex with men (MSM). In Peru, MSM have an HIV seroprevalence 40 times higher than the rest of the population, and high-risk MSM experience a 2.2–3.5% HIV incidence rate, compared with a 0.4% in the general population.

Comparison between inner and outer foreskin showed no differences in the tissue homeostasis and keratinocyte proliferation, but the inner foreskin layer was thinner than outer foreskin in the studied population. This difference was relatively small and not consistently reported in previous studies; moreover, this observation alone cannot completely explain the decreased susceptibility to HIV-1 in circumcised men.

Mucosal inflammation has been recognized in several studies as a risk factor for HIV-1 acquisition, since the virus, although capable of infecting quiescent cells, replicates more efficiently in activated cells. Interestingly, the tight junctions between cells in the inner foreskin were reminiscent of inflammatory settings, as they resembled the organization identified by others in psoriatic skin. Furthermore, in vitro culture explants of inner and outer foreskin showed that inner foreskin secretes a higher amount of the three inflammatory markers IFN- γ , IP-10 and RANTES in the absence of stimulation. Finally, the inner foreskin contains an increased number of CD4+ CCR5+ T-cells, which are main targets for HIV-1 expressing the receptor (CD4) and one of the co-receptors (CCR5) needed for viral entry.

In conclusion, a more pro-inflammatory environment, including more potential HIV target cells, and reduced thickness of the inner foreskin, may explain the higher HIV susceptibility of uncircumcised men.

Dr. Lemos research is now focused on exploring whether specific inner foreskin microbiota triggers the recruitment of CD4+ CCR5+ cells. "If we can find the microbiota that increases inner foreskin permeability, inflammation and HIV target cell recruitment," explains Dr. Lemos, "we might better identify men at risk, and develop prevention strategies around controlling inflammation at this site."

[Lemos MP , Lama JR , Karuna ST , Fong Y , Montano SM , Ganoza C , Gottardo R , Sanchez J , McElrath MJ.](#) 2014. The Inner Foreskin of Healthy Males at Risk of HIV Infection Harbors Epithelial CD4+ CCR5+ Cells and Has Features of an Inflamed Epidermal Barrier. *PLoSOne*. 9(9): e108954

See also: [Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, Kiwanuka N, Moulton LH, Chaudhari MA, Chen MZ, Sewankambo NK, Wabwire-Mangen F, Bacon MC, Williams CF, Opendi F, Reynolds SJ, Laeyendecker O, Quinn TC, Wawer MJ.](#) 2007. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet*. 369(9562): 657–666.

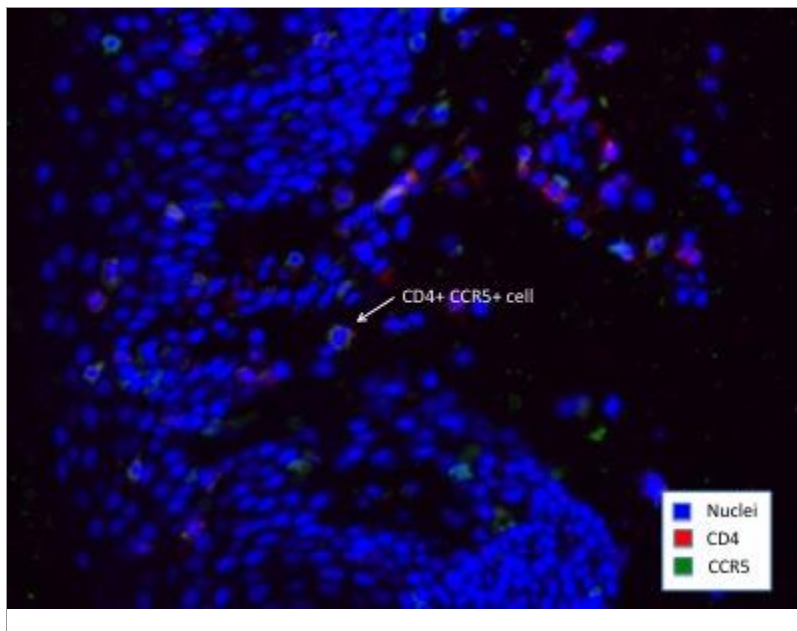


Image provided by Dr. Maria Lemos.

CD4+ T (red) and CCR5+ cells (green) in inner foreskin dermis and epidermis. DAPI is used to stain the nuclei of all cells. The arrow indicates a double positive cell.