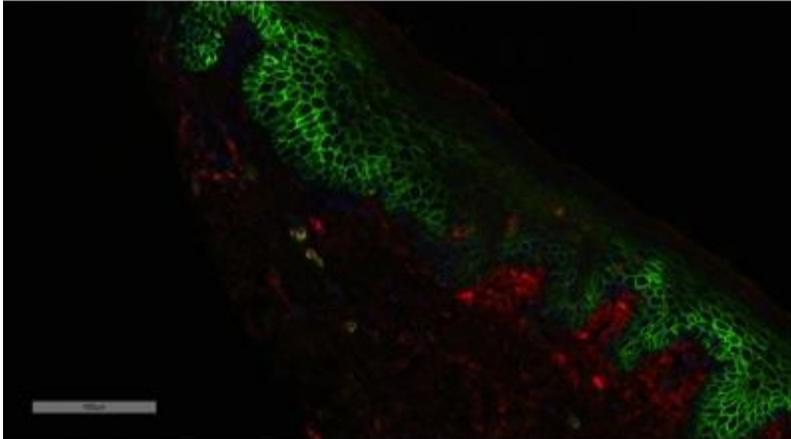


Conquering the outsides: an antibody story

December 20, 2015

L Pattacini



Immunohistochemistry staining of an inner foreskin sample, stained for CD138 (green, expressed by plasma cells and epithelial cells, and IgG (red), expressed by B cells and soluble in the tissue.

Image provided by Dr. Maria Lemos

This week, UNAIDS highlighted the need for encouraging a greater positive engagement of men in all aspects of the AIDS response and in advancing gender equality. Men and adolescent boys account for 52% of all new adult HIV infections. Around 60% of the 1.2 million people who died of AIDS-related illness in 2014 were male. A crucial site of HIV transmission in men is the foreskin, as confirmed by the observation that circumcision is protective against HIV acquisition.

The immune response at this site, and especially antibody production and transportation from the blood to the foreskin is poorly characterized. Antibodies, central molecules for our immune responses, are large Y-shaped proteins with antigen-binding and functional domains. Depending on the characteristics of this fraction we can distinguish different antibody isotypes: IgA, IgM, IgE and four types of IgG (IgG1, IgG2, IgG3 and IgG4), characterized by distinct functions. Each of these isotypes has a different capacity to neutralize pathogens, or activate complement, phagocytic cells, cytotoxic cells or NK cells.

Although the type of antibody response required for HIV protection is not completely understood, the HIV vaccine clinical trial RV144 or “ Thai trial” showed that risk for HIV infection directly correlates with the concentration of circulating IgA, whereas it is inversely correlated with IgG3 specific for Env V1V2 domain. Based on this finding, it is likely that a protective vaccine for HIV should be able to induce the production of such antibodies at the sites of HIV transmission. Two relevant aspects for vaccine design would be 1) to understand which antibody types are present at the mucosal site and

where they are produced and 2) to compare the antibody pattern in the blood and different mucosal sites, and to identify the tissues that should be studied during a vaccine trial. Research associate Dr. Maria Lemos, from the Vaccine and Infectious Disease Division at Fred Hutch, decided to take the challenge and answer these questions. The results of the study have been published in the November issue of *Mucosal Immunology*.

An interesting finding coming out from Dr. Lemos' work is that antibody distribution and concentration in the colon is not a proxy for foreskin, as it might not be for other mucosal tissues. In particular, IgA concentration is fourfold greater in colon than in the foreskin, whereas IgG concentration is higher in the foreskin as compared to colon.

Foreskin antibodies derive in part from the blood, and in part are locally produced by IgM-, IgG- and IgA-secreting cells located in the foreskin dermis, which are detectable (as shown in the Figure) as single cells but not organized in cell follicles. Since part of the antibodies detected in the foreskin is in the transudate from blood, it is possible that vaccination-produced antibodies can reach the epidermal layer of the foreskin, where the contact with the virus is more likely to happen prior to actual infection. Although the majority of antibody isotypes were primarily located in the dermal layer and did not reach the epidermis, IgG1, IgG2 and IgG3 ratios were comparable between the two layers. This is especially interesting considering that Env-specific IgG3 have been shown protective against HIV acquisition in RV144. To evaluate whether it would be possible to characterize antigen-specific responses in the different foreskin layers, the presence of Adenovirus 5-specific antibodies was evaluated. Ad5 antibodies were present in the inner foreskin epidermis, and were primarily derived from the blood.

"I think there are two important lessons highlighted in this paper that contribute to vaccine design" said Dr. Lemos. "The first is that antibody immunity at the gut does not necessarily represent immunity at genital surfaces of the penis, so upon vaccination, it might be useful to characterize the two compartments. The second is that some antibodies do appear to locate in the epidermis of the inner foreskin, which suggest they might contribute to protection at this site." The results obtained are encouraging in view of the design of a vaccine that can generate mucosal responses in a site of HIV transmission.

The research was supported by grants from the National Institute of Allergy and Infectious Disease of the National Institutes of Health and from the University of Washington Center for AIDS Research.

[Lemos MP, Karuna ST, Mize GJ, Fong Y, Montano SM, Ganoza C, Lama JR, Sanchez J, McElrath MJ.](#) 2015. In men at risk of HIV infection, IgM, IgG1, IgG3, and IgA reach the human foreskin epidermis. *Mucosal immunology*. doi: 10.1038/mi.2015.103. [Epub ahead of print.]