

Monday, 4th August, 16h30-18h

The mechanism of sexual transmission of human immunodeficiency virus (HIV-1) via the foreskin epithelium

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Résumé:

Background: The first steps of sexual transmission of the human-immunodeficiency-virus (HIV) at different mucosal sites involve transport of HIV across epithelial barriers covering the skin / mucosal surfaces, including the male genitals. Although male circumcision was reported to reduce male acquisition of HIV by >60%, the initial mechanism of HIV transmission at the male genitals remains elusive. A chief problem in studying the early phases of foreskin HIV infection is the lack of proper in-vitro model systems that reflect the in-vivo architecture.

Methods: We established a novel in-vitro immunocompetent model of the human foreskin. It includes a fibrous sheet produced by foreskin fibroblasts that are topped by differentiating keratinocytes, from either inner/outer aspects of the foreskin. Dendritic cells (DCs) and/or Langerhans cells (LCs) are further integrated into the model. In parallel, we also developed an ex-vivo polarized foreskin explant model.

Results: We found that upon apical exposure to cell-associated HIV, virus particles translocate rapidly across reconstructions, while translocation of cell-free HIV is extremely limited. Moreover, HIV is translocated more efficiently via:

- 1) reconstructions produced with keratinocytes from inner foreskin;
- 2) reconstructions integrating DCs/LCs.

In addition, ex-vivo exposure of normal foreskin explants to cell-associated HIV results in entrapment of viral particles in the thicker keratin layer of the outer foreskin, along with migration of LCs to the upper epithelium sending dendrites to the lumen. Finally, seminal plasma (SP) from HIV-negative men mixed with cervico-vaginal secretions (CVS) from HIV-positive women, which mimics the in-vivo mixture of these genital secretions during woman-to-man HIV sexual transmission, decreased HIV infection at the foreskin.

Conclusions: Our findings suggest an active role of DCs/LCs in sampling of luminal virus followed by their migration out of the epithelium. This process is more efficient at the inner aspect of the foreskin, and may be inhibited by yet ill-defined components present in SP/CVS.