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Oral presentation

OA011-01. Early events of human immunodeficiency virus type 1 (HIV-1) *ex vivo* penetration in the foreskin mimicking HIV-1 sexual transmission

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Background

Although male circumcision was reported to reduce male acquisition of HIV-1 by 60%, the initial mechanisms of HIV-1 transmission at the male genitals remain elusive. A chief problem in studying the early phases of foreskin HIV-1 infection is the lack of proper *in vitro* model systems that reflect the *in vivo* architecture.

Methods

Two novel models of the adult human foreskin mucosa were established: 1) *ex vivo* polarized inner and outer foreskin explants; 2) *in vitro* immuno-competent reconstructed foreskins, which include fibrous sheets produced by foreskin fibroblasts that are topped by differentiating foreskin keratinocytes (from either inner or outer foreskin) and Langerhans cells (LCs). These models permit to inoculate comparatively in a polarized manner at the mucosal pole either HIV-1-infected cells (that are present in all secretions vectorizing HIV-1) or cell-free HIV-1.

Results

Efficient HIV-1 transmission occurs following 1 hr exposure of the inner, but not outer, foreskin to cells highly infected with HIV-1. Such HIV-1-infected cells form viral synapses with mucosal/apical foreskin keratinocytes, leading to polarized budding of the virus. In inner foreskin, HIV-1 is in turn rapidly internalized by LCs that migrate to the epidermal-dermal interface. There, LCs form conjugates with T-cells thereby transferring HIV-1. Cell-free HIV-1 is inefficient at foreskin penetration. To mimic the *in vivo* mixture of genital fluids during woman-to-man HIV-1 sexual transmission, the effect of a mixture of seminal plasma from HIV-negative men mixed with cervico-vaginal secretions from HIV-positive women was investigated. Such mixture significantly reduced HIV-1 translocation in inner foreskin reconstructions.

Conclusion

LCs have an active role in sampling HIV-1 at the foreskin followed by transfer of virus to T-cells. This process is highly efficient in the inner foreskin and when HIV-1 originates from infected cells. This process is blocked by yet ill-defined components activated when mixing genital fluids.