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Institutionen för medicin, Solna

HIV target cells and innate immune factors in the human female genital tract

AKADEMISK AVHANDLING
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av

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ABSTRACT

World-wide, human immunodeficiency virus (HIV) transmission most often takes place in the genital tract during heterosexual intercourse, but the site where HIV most commonly establishes primary infection in the female genital tract remains unknown. Several factors including viral load in the HIV-infected individual, presence of genital infections, genotype and possibly sex hormone levels influence the risk of HIV acquisition. In addition, cationic polypeptides with anti-HIV activity in vitro including secretory leukocyte protease inhibitor (SLPI), Elafin/Trappin-2, human neutrophil peptide (HNP) 1-3 and LL-37 may play dual roles in vivo with both an antiviral effect and target cell-recruiting properties.

For this thesis, we investigated the distribution of potential HIV target cells in three anatomical regions (ectocervix, endocervix and endometrium) of the female genital tract by immunostaining, computerized image analysis and confocal microscopy. Furthermore, innate immune peptides were quantified in genital secretions using ELISA and in ectocervical tissue using real-time RT-PCR and immunohistochemistry. To characterize antigen presenting cell subsets and their expression of HIV-binding C-type lectin receptors (CLRs) ectocervical tissue biopsies were collected from HIV-negative women at low-risk of HIV infection and HIV-negative female sex workers considered to be at high-risk of acquiring such infection. Distinct cell populations were identified including $CD1a^+$ $Langerin^+$ Langerhans cells (LCs) in the epithelium and $CD11c^+$ $DC\text{-}SIGN^+$ myeloid dendritic cells (mDCs), $CD68^+$ $DC\text{-}SIGN^+$ Mannose $receptor^+$ (MR^+) mDCs and/or macrophages as well as $CD123^+$ plasmacytoid dendritic cells (pDCs) in the submucosa of the ectocervix. The high-risk women had significantly higher expression of CLRs than the low-risk subjects. To map the distribution of potential cellular targets and receptors binding to HIV in the endocervix and endometrium, tissue biopsies were collected from HIV-uninfected low-risk women undergoing hysterectomy. LCs were localized mainly in the columnar epithelium, whereas $CD4^+$ $CCR5^+$ T cells were present both within and adjacent to the endometrial and endocervical epithelium. $CD11c^+$ $DC\text{-}SIGN^+$ MR^+ and $CD68^+$ $DC\text{-}SIGN^+$ MR^+ mDCs and macrophages were confined to the submucosa of both tissue types but were localized in close proximity to the epithelial surface. To assess the expression of SLPI, Trappin-2, HNP 1-3 and LL-37, genital fluid samples and ectocervical biopsies were collected from HIV-uninfected low-risk woman and HIV-uninfected sex workers (HIV high-risk). LL-37 and Trappin-2 levels were significantly lower among low-risk women currently using combined oral contraception. Compartmentalization of the investigated factors classed HNP 1-3 as the most abundant factor in genital fluids of low-risk woman, whereas SLPI had the highest expression in ectocervical tissue. No association between tissue expression and soluble levels of the investigated factors was seen at the individual level in either HIV low-risk or high-risk women.

In summary, the spatial distribution of potential HIV target cells and innate immune factors may play an important role in HIV transmission events. Thus, a better understanding of this environment may contribute to designing HIV-inhibiting compounds.