



**Karolinska
Institutet**

Institutionen för Medicin, Solna

BIOLOGY OF HIV TRANSMISSION AND ANTIVIRAL MUCOSAL IMMUNITY IN THE FEMALE GENITAL TRACT

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska
Institutet offentligen försvaras i Nanna Svartz Aula, A1:00,
Karolinska Universitetssjukhuset

Fredagen den 2 mars, 2012, kl 09.00

av

Pauline Levinson

Läkare

Huvudhandledare:

Professor Kristina Broliden
Karolinska Institutet
Institutionen för Medicin, Solna

Bihandledare:

Doktor Taha Hirbod
Karolinska Institutet
Institutionen för Medicin, Solna

Fakultetsopponent:

Universitetslektor Marianne Jansson
Lunds Universitet
Institutionen för Laboratiemedicin

Betygsnämnd:

Professor Jan Albert
Karolinska Institutet
Institutionen för Mikrobiologi, Tumörbiologi
och Cellbiologi

Professor emerita Gunnel Biberfeld
Karolinska Institutet
Institutionen för Mikrobiologi, Tumörbiologi
och Cellbiologi

Professor Bo Svennerholm
Göteborgs Universitet
Institutionen för Biomedicin

Stockholm 2012

ABSTRACT

Human immunodeficiency virus (HIV) is primarily transmitted through heterosexual intercourse and women in Sub-Saharan Africa are disproportionately affected. Correlates of protective immunity and mucosal factors influencing sexual HIV transmission need to be identified as they may serve as critical targets for HIV intervention. The aim of this thesis was to determine whether IgA antibodies and antimicrobial peptides contribute to mucosal immune defence in individuals who are at high risk of acquiring HIV.

Our understanding of the role of mucosal immunology in HIV transmission has been gained from studies of cohorts of highly HIV-exposed seronegative (HESN) individuals. The studies in the present thesis are based on clinical samples from well-characterized cohorts of Kenyan HESN individuals, including female sex workers and HIV serodiscordant couples (where one partner is HIV-positive and the other is HIV-negative).

Baseline cervicovaginal secretion (CVS) samples from HIV-negative female sex workers were analysed for levels of antimicrobial peptides with HIV neutralizing activity and the results were compared with subsequent HIV seroconversion. We found that the antimicrobial peptides HNP1-3 and LL-37 correlated with the *in vitro* HIV neutralizing activity of CVS. However, despite the *in vitro* HIV neutralizing properties of HNP1-3 and LL-37, higher levels of these peptides were associated with increased HIV acquisition. It is possible that elevated levels of these peptides were induced by sexually transmitted infections (STIs) and, even though the peptides neutralized HIV to some extent, the overall STI-associated inflammation resulted in susceptibility to HIV infection. In the same cohort, elevated levels of the antimicrobial peptide Trappin-2 were associated with reduced HIV acquisition.

In a prospective clinical study of HIV-discordant couples, CVS was obtained from three groups including HESN, HIV-positive and low-risk control women. Levels of selected antimicrobial peptides in CVS were comparable between the groups. However, elevated levels of HNP1-3 and LL-37 in the HESN women correlated with a higher viral load in the HIV-infected male partner. When analysing the humoral immune response we found that HESN women were five times more likely to have HIV neutralizing IgA detected in their CVS than low-risk controls. Unexpectedly, the presence of neutralizing IgA was inversely correlated to the male partner's viral load.

In conclusion, a significant proportion of HESN women displayed HIV neutralizing genital IgA compared to control women. Furthermore, the HIV neutralizing capacity of CVS correlated with subsets of specific antimicrobial peptides, although detection of high levels of antimicrobial molecules in clinical samples is not necessarily a marker of protection against HIV. Hence, the humoral immunity and the dual role of antimicrobial peptides, including their antiviral and proinflammatory properties, should be carefully evaluated in future clinical trials of preventive strategies against sexual HIV transmission.

ISBN 978-91-7457-654-2