Genital immunology, the microbiota and HIV transmission

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Overview

- Genital mucosal inflammation
  - Association with HIV acquisition
- Co-infections and genital microbiome have important mucosal impacts
  - May enhance mucosal homing of susceptible T cells
  - And/or induce cytokines that alter barrier function
- Important effects on HIV shedding in an HIV+ person
  - Not covered today

Mucosal HIV infection

Mucosal immune studies

- Sigmoid colon studies in Toronto
- Foreskin studies in Rakai, Uganda
- Cervical studies in Toronto, Nairobi

Mucosal CD4+ cells appear more HIV susceptible

- Cervix, other mucosal sites enriched for effector memory cells
- Much higher levels of immune activation
- HIV co-receptor & integrin expression


Enhanced virus entry in mucosal T cells

- Virus entry higher in cervix
- But blood, cervix correlated
- Enhanced in CD69+ and CCR5+ cells
- Also α4β7+, α4β1+ subsets

Mucosal inflammation and HIV risk

- Cervical α-defensins, cathelicidins associated with HIV acquisition in Kenyan women
  - despite in vitro antiviral effects
- Foreskin α-defensins associated with HIV acquisition in Ugandan men
- Cervical inflammatory cytokines associated with HIV acquisition in South African women


Foreskin cytokines and HIV acquisition

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INF-γ</td>
<td>2.26 (1.32, 3.86)</td>
<td>2.00 (1.23, 3.22)</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>2.00 (1.13, 3.56)</td>
<td>1.23 (0.72, 2.10)</td>
</tr>
<tr>
<td>IFNg</td>
<td>2.00 (1.08, 3.73)</td>
<td>1.23 (0.72, 2.10)</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.90 (1.09, 3.24)</td>
<td>1.23 (0.72, 2.10)</td>
</tr>
<tr>
<td>IL-8</td>
<td>1.70 (0.95, 3.02)</td>
<td>1.23 (0.72, 2.10)</td>
</tr>
<tr>
<td>TNFα</td>
<td>1.60 (0.88, 2.88)</td>
<td>1.23 (0.72, 2.10)</td>
</tr>
</tbody>
</table>

*Conditional logistic regression, matched by site, controlling for age, BMI,dbcystitis and HIV status, and all variables associated with either circumcision or U=4 HIV transmission (occupation, marital status, travel multiple countries, random use, consumption of alcohol).

- Foreskin swabs collected during Rakai clinical trial of MC
  - 60 men who acquired HIV and 120 uninfected controls
- Levels of many cytokines low; more IL-8 (aOR 2.6) and MIG (aOR 3.1) among men who subsequently acquired HIV

Prodger J, CROI 2014.

How is genital inflammation increasing susceptibility?

- N=96 HIV neg Kenyan women
- Inflammation if ≥3/7 pro-inflammatory cytokines in upper quartile (n=28)
- Cytobrush (cell studies) and CVL (proteomics)

Arnold K and Burgener A. Muc Immuno, 2015.

Mucosal effects of genital inflammation: proteomic analysis

- CD4+ cell numbers doubled in the context of inflammation
- Proteome also altered: some parameters increased, others lower

Arnold K et al. Muc Immuno, 2015.

Proteomic associations of FGT inflammation

- Up-regulation of neutrophil proteases, cell motility, actin cytoskeleton
- Down-regulation of antiproteases, keratinization, epithelial differentiation

Immune associations of clinical conditions that enhance HIV risk

- Several clinical conditions consistently associated with increased HIV acquisition risk

1. Asymptomatic HSV-2 infection (OR=2.8-3.4)
2. Bacterial vaginosis, ie: disruption in ‘normal’ vaginal microbiota (OR=1.6)

Asymptomatic HSV2 and genital immunology

- Studies in Toronto ACB women (n=46)
  - increased α4β7 expression in blood
  - α4β7+ cells are more activated
  - direct correlation with more activated cervical CD4 T cells
  - BUT no association with CV cytokines


Summary

- Genital mucosal inflammation
  - (i) recruits HIV susceptible target cells, and (ii) alters epithelial integrity
  - possibly mediated via different effector cytokines

- Often these things happen together, but not necessarily
  - HSV2: increased HIV target cell numbers without inflammatory cytokines
  - Dysbiosis: increased inflammatory cytokines without cell number/subset alterations

- Possible implications for populations where both are common, esp. ACB women