HSV-2-driven changes in $\alpha_4\beta_7$ expression correlate with increased susceptibility to SHIV

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HSV-2 Increases Risk of HIV-1 Acquisition

Even in absence of detectable HSV-2 replication, inflammation and lesions.

- HSV-2 as *tool* to investigate changes that correlate with susceptibility to HIV infection

  - HSV-2 rectal infection increases the % of $\alpha_4\beta_7^{\text{high}}$ CD4$^+$ T cells in the rectal tissue (Martinelli et al. Plos Path 2011)
  
  - SIV acquisition correlates with the % of $\alpha_4\beta_7^{\text{high}}$ CD4$^+$ T cells before challenge (Martinelli et al. J AIDS 2013)
What About Vaginal Infection?
HSV-2 Infected Macaques are More Susceptible to Vaginal SHIV Infection

1 vaginal challenge: 250 TCID$_{50}$ of SHIV$_{SF162P3}$

<table>
<thead>
<tr>
<th>HSV-2</th>
<th>SHIV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>POS</td>
<td>4/5</td>
</tr>
<tr>
<td>NEG</td>
<td>1/5</td>
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</tbody>
</table>

Blood/Swabs (tested for HSV-2)
HSV-2 Increases the % of $\alpha_4\beta_7^{\text{high}}$ CD4$^+$ T cells in Vaginal Tissue

**VAG**

- % $\alpha_4\beta_7^{\text{high}}$
- % CCR5
- % CD103

**BLOOD**

- % $\alpha_4\beta_7^{\text{high}}$
- % CCR5
- % CD103

p-values: 0.055, 0.309
The % of $\alpha_4\beta_7^{\text{high}}$ CD4$^+$ T Cells in Blood and Vaginal Tissue do not Correlate
HSV-2 Infection Increases Expression of $\alpha_4\beta_7$ and CD11c on Vaginal DCs

**VAG**

- **MFI $\alpha_4\beta_7$**
  - NEG: [Graph]
  - POS: [Graph]
  - $p = 0.027$

- **MFI CD103**
  - NEG: [Graph]
  - POS: [Graph]
  - $p = 0.055$

- **MFI CD11c**
  - NEG: [Graph]
  - POS: [Graph]
  - $p = 0.008$

**BLOOD**

- **MFI $\alpha_4\beta_7$**
  - NEG: [Graph]
  - POS: [Graph]
  - $p = 0.150$

- **MFI CD103**
  - NEG: [Graph]
  - POS: [Graph]
  - $p = 0.095$

- **MFI CD11c**
  - NEG: [Graph]
  - POS: [Graph]
  - $p = 0.031$
HSV-2-driven changes in vaginal mucosa correlate with susceptibility to SHIV?
Ex Vivo HSV-2 Infection of Macaque Vaginal Tissue

HSV-2 ± ACV 3hrs

Vaginal BX

wash

HSV-2 ± ACV 3hrs

18hrs or 3 days
Ex Vivo HSV-2 Increases the % of $\alpha_4\beta_7^{\text{high}}$ and CD103$^+$ CD4$^+$ T cells in Vaginal Mucosa
Ex Vivo HSV-2 Increases the % of $\alpha_4\beta_7^{\text{high}}$ CD80$^+$ CD3$^-$ HLA-DR$^+$ in the Vaginal Mucosa

![Graph showing % $\alpha_4\beta_7^{\text{high}}$ CD80 with ACV and non-ACV groups, with p=0.012.]

![Graph showing HSV-2 copies/ml versus % $\alpha_4\beta_7^{\text{high}}$ CD80, with p=0.002.]

Ex Vivo HSV-2 Infection Increases the Susceptibility of the Vaginal Mucosa to SHIV

![Graph showing increased SIV-gag/ml in SHIV + HSV-2 compared to SHIV alone. The p-value is 0.013.](image)
SHIV Infection Correlates with the HSV-2-Driven Increase in % of $\alpha_4\beta_7^{\text{high}}$ CD4$^+$ T cells

![Graph showing correlation between SIV-gag/ml (10$^3$) and fold (% $\alpha_4\beta_7^{\text{high}}$). The p-value is 0.020.](image)
Base Line $\alpha_4\beta_7$ expression Correlates with SHIV infection Ex Vivo

Independent of HSV-2 infection
Summary:

• HSV-2 chronically infected macaques:
  – More susceptible to SHIV infection.
  – Higher % of $\alpha_4\beta_7^{\text{high}}$ CD4$^+$ T cells in vaginal tissue
  – Higher $\alpha_4\beta_7$ expression on vaginal DCs
  – More inflammatory factors in vaginal fluids

• HSV-2 infection of vaginal tissue ex vivo:
  – Increases SHIV replication
  – Increases the % of $\alpha_4\beta_7^{\text{high}}$ CD4$^+$ T cells and $\alpha_4\beta_7^{\text{high}}$ CD80$^+$ APCs
  – Increased $\alpha_4\beta_7^{\text{high}}$ CD4$^+$ T correlate with SHIV replication in HSV-2/SHIV infected tissues.
Summary:

- Ex vivo SIV replication correlates with:
  - BL expression of $\alpha_4\beta_7$ on $\alpha_4\beta_7^{\text{high}}$ CD4 T cells
  - Frequency of $\alpha_4\beta_7^+$ CD4 T cells.

*Availability of $\alpha_4\beta_7^+$ cells facilitates HIV infection?*
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