Th22 cells and IL-22 production in HIV-associated gut immunopathogenesis

Gastrointestinal mucosa and HIV

- HIV infection is associated with immunological and structural damage to and within the gut mucosa.

- Microbial products cross the gut mucosa and enter the blood circulation, increasing systemic immune activation and driving HIV disease progression.

Rhesus Macaque Colon - Cytokeratin / E.coli / DAPI

Estes et al., Plos Path 2010
Brenchley et al., Nat Med 2007
A compromised gastrointestinal mucosa may contribute to HIV disease progression.

- **Structural Loss**
  - Increased Permeability
  - Microbial Translocation

- **Immunological Loss**
  - Local Bacterial Persistence
  - Bacteremia
  - Immune Activation
  - Disease Progression
Th22 cells and IL-22 producing cells

- A new CD4 subset defined by the production of IL-22, independent of Th1, Th2, or Th17-associated cytokines.

- The cytokine IL-22 acts on non-immune (including epithelial) cells and has repair/regenerative properties.

- HIV impact is unclear.
Blood Th22 cells and HIV infection

- Blood Th22 cells in HIV uninfected individuals express higher frequency and density of HIV co-receptor CCR5 and HIV binding molecule α4β7 than other CD4 subsets.

- Blood Th22 cells tended to lose the high expression of these molecules in HIV infected individuals.
### Sigmoid study group characteristics

<table>
<thead>
<tr>
<th></th>
<th>HIV uninfected</th>
<th>Chronic infection, untreated</th>
<th>Long-term ART treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV- (N=8)</td>
<td>HIV+ (N=11)</td>
<td>HIV+ART (N=16)</td>
</tr>
<tr>
<td><strong>CD4 count (c/ml)</strong></td>
<td>750.0</td>
<td>280.0</td>
<td>660.0</td>
</tr>
<tr>
<td><strong>Blood VL (c/ml)</strong></td>
<td>--</td>
<td>39,967</td>
<td>&lt;50</td>
</tr>
<tr>
<td><strong>Dur. ART (yrs)</strong></td>
<td>--</td>
<td>--</td>
<td>12.5</td>
</tr>
<tr>
<td><strong>Dur. Aviremia (yrs)</strong></td>
<td>--</td>
<td>--</td>
<td>10.0</td>
</tr>
</tbody>
</table>
Sigmoid Th22 cells were depleted in HIV infection.

**A**

- Absolute Th22 cells (Milli/g)
- HIV- 0.15
- HIV+ 0.10
- HIV+ART 0.05
- P=0.712
- P=0.013
- P=0.025

**B**

- CD4
- IL-22
- HIV- 0.9
- HIV+ 0.0
- HIV+ART 1.3

**C**

- CD3 DAPI
- CCR10 DAPI
- CD3 CCR10 DAPI
- CD3 CCR10

**HIV-**

- Arrows indicating cell presence

**HIV+**

- Arrows indicating cell absence
Non-T cell sources of sigmoid IL-22 in untreated HIV infection

**A**

<table>
<thead>
<tr>
<th></th>
<th>HIV-</th>
<th>HIV+</th>
<th>HIV+ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>0.1</td>
<td>1.28</td>
<td>0.385</td>
</tr>
<tr>
<td>IL-22</td>
<td>47.9</td>
<td>52.7</td>
<td>41.7</td>
</tr>
</tbody>
</table>

**B**

Proportion of IL-22 from CD3(-) to CD3+ Gut lymphocytes

- P = 0.680
- P = 0.351
- P = 0.251
Reduced epithelial integrity during untreated HIV infection

<table>
<thead>
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<th>HIV-</th>
<th>HIV+</th>
<th>HIV+ART</th>
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</thead>
</table>

100 μm
Sigmoid Th22 cells and IL-22 producing capacity correlated with improved epithelial integrity in HIV infected individuals

(A) HIV+ART

(B) HIV+

%Z0-1 (to relative control)

% Gut Th22 cells

P=0.027

r_s=0.587

IL-22 producers from CD3- cells

Gut lymphocytes

P=0.034
Exogenous IL-22 protected against HIV-induced epithelial integrity loss *in vitro*
1. Blood Th22 cells express an HIV susceptible surface phenotype that is not apparent in HIV infection.

2. Sigmoid Th22 cells and IL-22 producing capacity is lost in HIV infection and reconstituted in long-term ART treatment.

3. Both Th22 cells and IL-22 production by other mucosal cells correlated with enhanced epithelial integrity.
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