Transcriptional profiling of the host response to SIV infection in Rhesus Macaques and Sooty Mangabeys

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“For this field to make progress, we need to become evolutionist and learn more about natural SIV hosts. We need to think about ways to harness the human immune system to adapt to the virus in the same way.”

Dr. Warner Greene, Chair - Final Remarks of the NIAID Summit on AIDS Vaccines, Bethesda, March 25th 2008.
Sooty Mangabeys are a natural host of SIV infection

- West African monkeys, natural reservoir of SIVsmm
- SIVsmm is the origin of HIV-2 and SIVmac viruses
- Infection common in the wild and in captivity

**SIVsmm infection**
- Absence of disease
- Chronic high viral load \((10^4-10^6\text{ copies/ml})\)
- Preservation of blood CD4+ cell in >90% of animals
- Low levels of T cell activation, proliferation and apoptosis

**Disease resistance is not due to:**
- Reduced virus cytopathicity
- Restricted virus tropism
- Better adaptive antiviral immune responses
## Comparative studies of natural vs non-natural host SIV infection

<table>
<thead>
<tr>
<th>Species</th>
<th>Non-Natural</th>
<th>Natural</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rhesus Macaque</td>
<td>Sooty Mangabey</td>
</tr>
<tr>
<td>Disease</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Viremia</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>CD4 depletion blood</td>
<td>Yes</td>
<td>Rare</td>
</tr>
<tr>
<td>CD4+ depletion gut</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute Immune Activation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic Immune Activation</td>
<td>Yes</td>
<td>No</td>
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Objectives

1. Compare the profile of gene expression during acute and chronic SIV infection of sooty mangabeys and rhesus macaques.

2. Identify molecular pathways involved in the differential regulation of the host immune responses in the two species.
Experimental Design

- **Whole blood RNA collection:**
  - 5 RMs
  - Acute (d) -5, 3, 7, 10, 14, 30
  - Chronic (d) 180

- **Data analysis:**
  - 5 SMs
  - 8 RMs

- **Affymetrix Rhesus arrays:**

- **SIVsmm:**
  - in progress

- **SIVmac239:**
  - in progress

**Table:**

<table>
<thead>
<tr>
<th>Type</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (d)</td>
<td>-5, 3, 7, 10, 14, 30</td>
</tr>
<tr>
<td>Chronic (d)</td>
<td>180</td>
</tr>
</tbody>
</table>
Gene expression is fundamentally different between host species

Principal Component Analysis
All present genes

ANOVA
Genes regulated by SIVsmm infection

Species
SM  RM

Rhesus  Mangabey

<table>
<thead>
<tr>
<th></th>
<th>Rhesus</th>
<th>Mangabey</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
<td>4252</td>
<td>1634</td>
</tr>
<tr>
<td>Percent</td>
<td>25%</td>
<td>41%</td>
</tr>
</tbody>
</table>

5886 – 25%  8095 – 41%
SIV induced genes clustered by expression pattern

Species
- SM
- RM

Infection
- Uninfected
- Acute – 3-30 d
- Chronic – 180 d

Log Intensity

10.1
8.2
3.5
Type I Interferon Stimulated Genes (ISGs) induced during SIV infection

Species
- SM
- RM

Infection
- Uninfected
- Acute – 3-30 d
- Chronic – 180 d

Log Intensity
- 10.1
- 8.2
- 3.5

Post Acute
ISG expression in SMs during SIVsmm infection

1. We observed a strong (~4-5 log), but transient induction in Type I interferon stimulated genes (ISGs) in SMs during acute SIVsmm infection

2. SM pDCs produce lower amounts of IFNα in response to TLR7/9 ligands than RM (Mandl et al., 2008)

3. The clear upregulation of ISG expression in SMs observed in the current study may be related to:
   • IFNα production by other cell types and/or in response to other stimuli
   • Threshold of TLR7/9 activation may be lower during acute SIV infection

4. Low IFNα production by pDCs and down-regulation of ISGs may prevent systemic immune activation during chronic SIV infection of SMs
Preliminary Conclusions:

- SIV induced gene expression is fundamentally different between SM and RM.

- SMs exhibit a robust but transient up-regulation of ISG mRNA during acute infection.

- Previously unrecognized genes involved in the host response to SIV in SMs are currently being identified.
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