Impact of SIGLEC-1 null variant on disseminated tuberculosis during HIV-1 co-infection
Siglec-1 modulates immune responses

Siglec-1 mediates HIV-1 capture and *trans*-infection

Siglec-1 truncating variants in humans

Identification of Siglec-1 null individuals

HIV-1 SHCS cohort

<table>
<thead>
<tr>
<th>Null variant:</th>
<th>-/-</th>
<th>+/-</th>
<th>+/+</th>
</tr>
</thead>
<tbody>
<tr>
<td>n:</td>
<td>3,645</td>
<td>85</td>
<td>2</td>
</tr>
</tbody>
</table>

In collaboration with the SHCS

Siglec-1 null individuals do not transfer HIV-1

Siglec-1 null individuals have a slower progression to AIDS

One of the Siglec-1 null individuals was co-infected with *M. tuberculosis*.

Adapted from Martinez-Picado et al. Nat. Communications (2016)
Could co-infections mask the potential beneficial effect we expect in HIV-1 mono-infection?
AIM

To investigate the effect of Siglec-1 truncation in HIV-1 related co-infections
TB is associated with Siglec-1 variant in the HIV-1 SHCS cohort

Table 1. Siglec-1 null variant and AIDS-defining infectious diseases in the HIV-1 SHCS cohort

<table>
<thead>
<tr>
<th>AIDS-defining infectious diseases</th>
<th>Null variant (heterozygous &amp; homozygous)</th>
<th>Wild type</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All bacterial diseases</td>
<td>7</td>
<td>138</td>
<td>0.0507</td>
</tr>
<tr>
<td><strong>Tuberculous mycobacterial diseases</strong></td>
<td><strong>5</strong></td>
<td><strong>54</strong></td>
<td><strong>0.0114</strong></td>
</tr>
<tr>
<td>Non-tuberculous mycobacterial diseases</td>
<td>1</td>
<td>24</td>
<td>0.4466</td>
</tr>
<tr>
<td>Other bacterial diseases</td>
<td>1</td>
<td>60</td>
<td>0.7656</td>
</tr>
<tr>
<td>All fungal diseases</td>
<td>10</td>
<td>452</td>
<td>0.6497</td>
</tr>
<tr>
<td>Pneumocystis pneumonia</td>
<td>3</td>
<td>235</td>
<td>0.9238</td>
</tr>
<tr>
<td>Other fungal diseases</td>
<td>7</td>
<td>217</td>
<td>0.2656</td>
</tr>
<tr>
<td>Viral diseases</td>
<td>2</td>
<td>192</td>
<td>0.9464</td>
</tr>
<tr>
<td>Protozoal diseases</td>
<td>1</td>
<td>57</td>
<td>0.7481</td>
</tr>
</tbody>
</table>
Disseminated TB is associated to the Siglec-1 null variant in a HIV-1 cohort

In collaboration with A. Telenti & P. McLaren (SHCS)
Siglec-1 knockout mice had more lung damage

Although bacillary load was similar in Siglec-1 knockout and wt mice

In collaboration with C. Vilaplana (UTE) and P. Crocker (Univ. Dundee)
Why is the loss-of-function variant of Siglec-1 gene associated to Mtb dissemination?

Immune control of Mtb via amplification of immune responses: EV exchange
Siglec-1 captures Extracellular Vesicles (EVs)

Could EVs derived from Mtb-infected cells follow this pathway?
EVs and Siglec-1 accumulate in the same compartment
EVs are captured by mDCs via Siglec-1

In collaboration with M. Monguíó (IGTP), L. Arias (UTE) and J. Chojnacki (Irsicaixa)
Only APCs capturing EVs via Siglec-1 triggered IFN-γ production on autologous PBMCs.
WT

Higher T cell responses

TB granulome

Lungs

Lympohoid tissues

Infected APC

CD4+ T cell

CD8+ T cell

Amplification of T cell responses via Extracellular Vesicles

Siglec-1

Cross-presentation

DC

Siglec-1 null

Lower T cell responses

TB granulome

Infected APC

CD4+ T cell

CD8+ T cell

Extracellular vesicles

Lack of antigen transfer via Extracellular Vesicles
HIV-1 & Exosomes trafficking in mature DCs

### Variant: 20:3687141 C / A

#### Population Frequencies

<table>
<thead>
<tr>
<th>Population</th>
<th>Allele Count</th>
<th>Allele Number</th>
<th>Number of Homozygotes</th>
<th>Allele Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>European (Non-Finnish)</td>
<td>851</td>
<td>65356</td>
<td>10</td>
<td>0.01302</td>
</tr>
<tr>
<td>South Asian</td>
<td>203</td>
<td>16498</td>
<td>5</td>
<td>0.0123</td>
</tr>
<tr>
<td>Latino</td>
<td>70</td>
<td>11528</td>
<td>1</td>
<td>0.006072</td>
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<tr>
<td>East Asian</td>
<td>34</td>
<td>8580</td>
<td>0</td>
<td>0.003963</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>880</td>
<td>0</td>
<td>0.005618</td>
</tr>
<tr>
<td>African</td>
<td>23</td>
<td>10144</td>
<td>0</td>
<td>0.002267</td>
</tr>
<tr>
<td>European (Finnish)</td>
<td>10</td>
<td>6548</td>
<td>0</td>
<td>0.001527</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1196</strong></td>
<td><strong>119544</strong></td>
<td><strong>16</strong></td>
<td><strong>0.01</strong></td>
</tr>
</tbody>
</table>
Bacillary load was similar in human Mtb-infected macrophages silenced or not for Siglec-1.

In collaboration with C Verollet et al (IPBS)
Siglec-1 does not interact directly with Mtb

In collaboration with M. Luquín (UAB) and M. Dupont (IPBS)
Production and isolation of fluorescent EVs derived from Mtb infected THP-1 cells

Adapted from:

In collaboration with M. Monguíó (IGTP) and L. Arias (UTE)
EVs are captured by mDCs via Siglec-1
EVs are captured by monocytes via Siglec-1

In collaboration with M. Monguíó (IGTP), L. Arias (UTE) and J. Chojnacki (Irsicaixa)
Siglec-1 mediates EVs capture and antigen transfer to lymphocytes