Background: How HIV controllers (HIC) maintain undetectable viremia without therapy is unknown. The strong CD4+ T cell HIV suppressive capacity found in many, but not all, HIC may contribute to long-lasting viral control. However, other earlier defence mechanisms may be involved. Here we examined intrinsic HIC cell resistance to HIV-1 infection.

Methods: 50 HIC from the ANRS C018 cohort, 43 healthy donors (HD), 9 chronic viremic patients (VR) and 12 HAART treated patients (ART) were included. The susceptibility to HIV-1 infection of monocyte-derived macrophages (MDM) and anti-CD3/CD28-activated CD4+ T cells was assessed by 5'-end-labeled HIV-1 proviral DNA PCR. The nucleofected MDM were induced to infect with HIV-1 BaL and expression of key restriction factors in MDM, macrophages and CD4+ T cells from HIC and HD was assessed.

Results: After in vitro challenge, monocyte-derived macrophages (p=0.003) and anti-CD3/CD28-activated CD4+ T cells (p=0.006) from HIC showed a reduced susceptibility to HIV-1 infection. This resistance was independent of HIV-1 co-receptor and selectively affected HIV-1 RNA synthesis (p=0.006). The susceptibility correlated with CD4+ T cell permissiveness to infection (Spearman 0.45, p=0.041; n=21). Restraint was not correlated with CD4+ T cell or monocyte activation and viral expression, but was correlated with the level of viral replication in one round infections with HIV-1/VSVG. Real-time PCR showed that the difference in the number of integrated copies matched the difference in the level of viral replication, pointing to restriction of productive infection. The restriction affected productive steps of HIV-1 replication and could be overcome by conditions enhancing infection (such as spinoculation and high cell density), suggesting the action of a saturable mechanism. Importantly, cell-associated HIV-1 RNA was detected at significantly lower levels in HIC (1.45 log copies/10^6 PBMC) and correlated with CD4+ T cell permisiveness to infection (Spearman 0.45, p=0.041; n=21).

Conclusions: CD4+ T cells and macrophages from HIC have a reduced susceptibility to HIV-1 infection. HIC, decreasing the difference in susceptibility to HIV-1 infection involves a restriction of productive infection in vitro irrespective of HIV-1 coreceptor usage.

Characteristics of the HIV-infected patients included in the study

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Sex</th>
<th>Last CD4</th>
<th>Last viral load</th>
<th>months on HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV controllers</td>
<td>50</td>
<td>M: 25 F: 25</td>
<td>540 (40-1025)</td>
<td>&lt;40 (&lt;40-365)</td>
<td>&lt;40 (&lt;40-365)</td>
</tr>
<tr>
<td>HIV-1 VR</td>
<td>9</td>
<td>M: 6 F: 3</td>
<td>378 (278-654)</td>
<td>42864 (8401-11606)</td>
<td></td>
</tr>
<tr>
<td>HAART treated</td>
<td>13</td>
<td>M: 10 F: 3</td>
<td>633 (292-880)</td>
<td>&lt;40 (&lt;40-51)</td>
<td>45 (7-90)</td>
</tr>
</tbody>
</table>

Macrophages and CD4+ T cells from HIC have a reduced susceptibility to HIV-1 infection

The reduced susceptibility of CD4+ T cells and macrophages from HIC was also observed during the first cycle of HIV-1 replication in one round infections with HIV-1/VS-G. Real-time PCR showed that their replication rate was lower than in HD. Moreover, p24 production vs HD was lower (p=0.006). Similar response to anti-CD3 stimulation

The block affects preintegrative steps of viral replication

The reduced susceptibility of CD4+ T cells and macrophages from HIC can be saturated by conditions enhancing infection (such as spinoculation and high cell density), suggesting the action of a saturable mechanism. Importantly, cell-associated HIV-1 RNA was detected at significantly lower levels in HIC (1.45 log copies/10^6 PBMC) and correlated with CD4+ T cell permisiveness to infection (Spearman 0.45, p=0.041; n=21).

Conclusions: CD4+ T cells and macrophages from HIC have a reduced susceptibility to HIV-1 infection. HIC, decreasing the difference in susceptibility to HIV-1 infection involves a restriction of productive infection in vitro irrespective of HIV-1 coreceptor usage.

Cell resistance also affects SIVmac and may be overcome by increasing viral inoculum and favoring cell-to-cell transmission, which suggests the implication of a saturable factor. Our results point to a contribution of intrinsic cell resistance to the control of infection and the containment of viral reservoir in HIC.

Macrophages and CD4+ T cell from HIC are resistant to HIV-1 in vitro in the PBMC of HIC, the level of viral replication in one round infections with HIV-1/VS-G. Real-time PCR showed that their replication rate was lower than in HD. Moreover, p24 production vs HD was lower (p=0.006). Similar response to anti-CD3 stimulation

The resistance of cells from HIC to HIV-1 infection is not associated to p21 expression

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The mechanical cell resistance to HIV in HIC can be saturated

HIC whose CD4 T cells were less susceptible to HIV-1 infection in vitro had also the lowest levels of cell-associated HIV-1 DNA in vivo. We found a positive correlation between the level of viral DNA in the PBMC of HIC and the level of HIV-1 replication in their CD4+ T cells infected in vitro (Spearman 0.457, p=0.047; n=19). This suggests that CD4 T cell resistance to HIV-1 may help to keep their viral reservoirs extremely low.

Conclusions: Macrophages and CD4+ T cell from HIC are resistant to HIV-1 infection in vitro irrespective of HIV-1 co-receptor usage. Cell resistance affects also SIVmac and may be overcome by increasing viral inoculum and favoring cell-to-cell transmission, which suggests the implication of a saturable factor. Our results point to a contribution of intrinsic cell resistance to the control of infection and the containment of viral reservoir in HIC.

INTRINSIC RESISTANCE TO HIV-1 OF MACROPHAGES AND CD4+ T CELLS FROM HIV CONTROLLERS

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