Effects of CCR5-Δ32 Heterozygosity on HIV-1 Reservoir Size and Immune Activation

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BACKGROUND

• HIV persists at a steady level during effective antiretroviral therapy and host factors that determine the level of HIV persistence are unknown
• CCR5-Δ32 heterozygosity (CCR5wt/Δ32) has been previously linked to long-term non-progression and protection from HIV acquisition

METHODS

• Allogeneic hematopoietic stem cell transplant; all three were CCR5 wt/Δ32
• Limited CCR5 expression on central memory CD4+ T cells helps protect sub-Marginal delays from pathogenic infection
• The Berlin Patient was cured and the Boston patients exhibited delayed viral rebound after HIV-1 pol DNA levels between CCR5 genotypes
• The Berlin Patient was cured and the Boston patients exhibited delayed viral rebound after

OBJECTIVE

To determine the impact of CCR5 surface expression on the HIV-1 reservoir

RESULTS

• CCR5 wt/Δ32 have lowered CCR5 cell surface expression in all CD4+ subsets
• No difference was observed in HIV-1 pol DNA levels between CCR5 genotypes
• Cell-associated HIV-1 RNA (p=0.035), HIV-1 RNA/DNA ratios (p=0.013), and frequency of detectable 2-LTR circle DNA (p=0.013) were significantly lower in CCR5 wt/Δ32
• Cell-associated HIV-1 RNA was significantly correlated with CCR5 cell surface expression on CD4+ T cells (r=0.136, p=0.002)
• No difference was observed in "ULTRA-DNA" and 5′S-DNA+ CD4+ cells and in CD4+ T cell subsets between the two CCR5 genotypes (data not shown)
• NF-κB pathway (IkBα, IKK) and target genes (IL-6, TNFα, IFNγ) were expressed at similar levels between genotypes (data not shown)

CONCLUSIONS

• The gene dosage effect of CCR5 Δ32 is seen equally in all CD4 subsets
• Limited CCR5 surface expression decreases HIV-1 transcription
• Limited CCR5 surface expression may suppress ongoing viral replication
• CCR5 surface expression does not impact NF-κB transcriptional potential
• Decreased CCR5 surface expression has different consequences than masking of CCR5 by marivirax

FUTURE DIRECTIONS

• Characterize the effects of CCR5 Δ32 on HIV-1 population genetics in ART-experienced individuals
• Determine if CCR5 surface expression modulates HIV-1 modulatory recombination in vitro models
• Examine the effects of CCR5 surface expression on the HIV-1 reservoir in lymphoid tissues

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References:


Table 1: Demographics and treatment history for study subjects

<table>
<thead>
<tr>
<th>Trait</th>
<th>CCR5 wt/Δ32</th>
<th>CCR5 Δ32</th>
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<tbody>
<tr>
<td>Number of subjects</td>
<td>1000</td>
<td>1000</td>
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<tr>
<td>Age at diagnosis (years)</td>
<td>50.1 ± 9.0</td>
<td>50.1 ± 9.0</td>
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<tr>
<td>CD4+ T cells at diagnosis (cells/μL)</td>
<td>500 ± 150</td>
<td>500 ± 150</td>
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<td>Time from diagnosis (years)</td>
<td>5.0 ± 2.0</td>
<td>5.0 ± 2.0</td>
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<tr>
<td>Early treatment duration (years)</td>
<td>5.0 ± 2.0</td>
<td>5.0 ± 2.0</td>
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Figure 1. CCR5 cell surface expression is decreased on CD4+ T cells in CCR5 wt/Δ32.

A. CCR5 Δ32 patients had significantly lower CCR5 cell surface expression (p=0.0154).

B. These patients had significantly lower CD4+ T cell counts (p=0.0722).

C. Subjects that initiated treatment during early infection and chronic infection were in open and closed circles, respectively.

Figure 2. Markers of ongoing viral replication in CD4+ T cells are reduced in CCR5 wt/Δ32.

A. CCR5 pol RNA and DNA levels were significantly lower in CCR5 wt/Δ32 (A). The frequency of CCR5- Δ32 CD4+ T cells was significantly lower in CCR5 wt/Δ32 (B). CCR5 Δ32 CD4+ T cell subset frequencies were lower in CCR5 wt/Δ32 (C).

B. Subjects initiated treatment during early infection and chronic infection were in open and closed circles, respectively.

Figure 3. Cell-associated HIV-1 RNA is significantly associated with CCR5 cell surface expression.

A. Cell-associated HIV-1 RNA was significantly correlated with CCR5 Δ32 (A) and with frequency of activated CD4+ T cells (B). Frequency of activated CD4+ T cells was correlated with CCR5 Δ32 (C). Subjects that initiated treatment during early infection were in open and closed circles, respectively.