Poster #448

CXCR4 Receptor Expression Is More Common on Activated CD4+ T Cells than CCR5 Expression in HIV-1 Infection

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Abstract

Background: Activated CD4+ T cells bearing chemokine coreceptors for HIV cell entry (CCR5 and/or CXCR4) are the primary targets for HIV replication, but the frequency of co-receptor expression on activated CD4+ T cells at varying CD4+ T cell counts has not been fully evaluated.
Methods: We performed multi-parameter flow cytometry to measure CD3, CD4, CD8, CCR5, CXCR4, CD38, and HLA-DR in 38 chronically infected persons with HIV-1 infection who were not on treatment. The median CD4 count was 503 cells/l (IQR 393, 600) and median VL was 36,460 copies/ml (IQR 7120, 56,776).
Results: There was a strong correlation between decreasing CD4+ T cell count and increased activation as measured by proportion of CD4+CD38+HLA-DR+ cells (r=0.48, p=0.002). In the overall group, of the activated (CD4+CD38+HLA-DR+) T cells, 39% were CXCR4+ alone, 33% were CCR5+CXCR4+, 16% were CCR5+ alone, and 12% had neither receptor. CD4+ T cell count decrease was associated with an increase in activated (CD38+HLA-DR+) CD4+ T cells that were CCR5-CXCR4+ (r=-0.41, p=0.012) and dual + (CCR5+CXCR4+ cells, r=-0.45, p=0.006) but there was a weaker correlation between CD4+ T cell count and CXCR4-CCR5+ CD4 cells (r=-0.3, p=0.07). The average ratio of CXCR4 to CCR5 expressing activated CD4+ T cells was 1.5 and did not vary significantly with CD4 count.
Conclusions: CXCR4 expression was more common on activated CD4+ T cells than CCR5 expression and this remained true with lower CD4 counts. Increases in the proportion of CD4+ T cells that were activated helped keep the absolute numbers of activated CD4 cells relatively stable with lower CD4 counts. As CD4+ T cell counts drop further, however, the predominance of CXCR4 expressing activated CD4 cells may provide more numerous targets for HIV replication that offer a survival advantage to HIV variants capable of using this chemokine receptor for cell entry.

Background

- The primary targets for infection by R5 HIV viruses are activated CD4+ T cells that express the CCR5 chemokine receptor, which serves as a co-receptor for HIV cell entry. X4 virus HIV infects activated CD4+ T cells expressing the CXCR4 chemokine receptor.
- While early HIV infection is characterized by R5 virus, dual tropic (virus capable of using both CCR5 and CXCR4 for cell entry) or mixed R5/X4 infection (with both R5 and X4 viral variants) is common in more advanced infection. The reason this change in tropism occurs is poorly understood. Although the emergence of X4 type virus is associated with rapid disease progression, it is not clear whether this is a *cause* of more rapid progression or a *consequence*.
- The frequency of co-receptor expression on *activated* CD4+ T cells at varying CD4+ T cell counts has not been fully evaluated. Multi-parameter flow cytometry methods allow more detailed characterization of activated T cell subsets.
- The relationship between T cell activation, co-receptor expression, and T cell counts is potentially important to understanding target cell availability, which may influence evolution of HIV tropism during disease progression, and may provide clues as to whether shifts in tropism may be a response to changes in target cell availability.

Methods

- We studied 38 chronically infected persons with HIV-1 who were not on treatment using baseline data from the Staying Well Study, an on-going randomized, controlled trial of the effects of meditation on HIV infection.
- We performed multi-parameter flow cytometry to measure CD3, CD4, CD8, CCR5, CXCR4, CD38, and HLA-DR on T cells using fresh blood specimens.
- The median CD4+ T cell count in persons studied was 503 cells/µl (IQR 393–600).
- The median viral load was 36,460 copies/ml (IQR 7120–56,776).

Results

- There was a strong correlation between decreasing CD4+ T cell count and increased activation as measured by proportion of CD4+CD38+HLA-DR+ cells (Figure 1).
- CXCR4 was more commonly expressed on activated (CD4+CD38+HLA-DR+) T cells than CCR5 (Figure 2). The average ratio of CXCR4 to CCR5 expressing activated CD4+ T cells was 1.5 and did not appear to vary substantially with CD4 count.
- When measured as a proportion of CD4+ T cells, lower CD4+ T cell counts were associated with a higher proportion of CD4+ T cells that were activated (CD38+HLA-DR+) and CCR5-CXCR4+ (r=-0.41, p=0.012) and activated and dual + (CCR5+CXCR4+ cells, r=-0.45, p=0.006), or CXCR4-CCR5+ CD4 cells (r=-0.3, p=0.07) (see Figure 2).
- The association of CD4 count with proportion of CD4 T cells that were activated and bore different chemokine receptors appeared to be primarily driven by the greater CD4+ T cell activation in participants with lower CD4+ T cell counts. When viewed as a proportion of activated CD4+ cells, the proportion with different chemokine receptor combinations was not substantially different at lower CD4+ T cell counts (Figure 3).
- Greater CD4+ T cell activation at lower CD4+ T cell counts did not fully compensate for the decrease in the number of CD4+ T cells, resulting in a lower total number of activated CD4+ T cells that are CCR5+ in the blood compartment in participants with lower CD4 + T cell count (Figure 4).

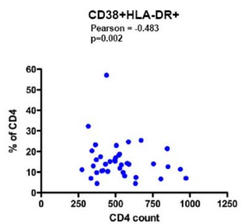

Figure 1: CD4+ activation (CD38+HLADR+) increases with lower CD4 counts

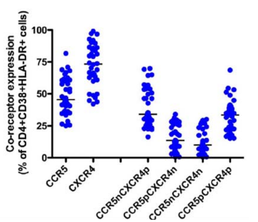

Figure 2: Fraction of activated (CD38+HLADR+) CD4+ T cells expressing CCR% and CXCR4

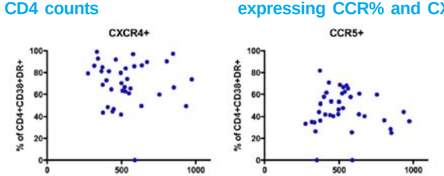

Figure 3: Proportion of activated CD4 T cells expressing CXCR4 or CCR5 expression by CD4 count

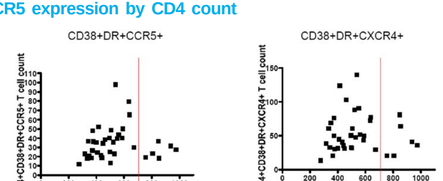

Figure 4: Relationship of activated CCR5 or CXCR4+ CD4+ T cells to CD4+ count
In participants with CD4 <700 cells/µl, r=0.57, p=0.001 for CCR5+ cells; r=0.32, p=0.09 for CXCR4+ cells

Conclusions

- CXCR4 expression was more common on activated CD4+ T cells than CCR5 expression and this remained true with lower CD4 counts.
- Greater CD4+ T cell activation may keep the absolute numbers of activated CD4 cells relatively stable with mildly decreased CD4 counts. As CD4+ T cell counts drop further, however, our cross-sectional data suggest that increases in activation no longer fully compensates and the total number of activated CD4+ T cells appears to drop.
- As the total number of activated CD4+ T cells that are targets for HIV replication declines with lower CD4+ T cell counts, the predominance of CXCR4-expressing activated CD4 cells over CCR5-expressing activated CD4+ T cells may provide an increasingly beneficial survival advantage to HIV variants capable of using this chemokine receptor for cell entry. This data is potentially consistent with the hypothesis that CD4+ T cell depletion favors the emergence of dual tropic virus due to target cell depletion. Additional longitudinal data from with patients with lower CD4+ T cell counts is needed to fully confirm this finding.

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