In patients on antiretroviral therapy

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Abstract

Background: Identifying a subset of T-cells that are enriched for HIV infection in patients on suppressive antiretroviral therapy (ART) will be critical to developing new curative strategies. This study aimed to assess how the expression of inflammatory (CCR5, CXCR3, CXCR4) and homeostatic (CCR6, CCR10) chemokine receptors (CRs) correlate with the size of the latent reservoir in patients receiving suppressive ART.

Methods: 40 subjects on ART for 3 years with HIV viral load <50 copies/mL were recruited in San Francisco. Using flow cytometry, we quantified the expression of the CR CXR5, CXCR3, CXCR4, and CCR6 and CCR7 on CD4+ T-cells. The corresponding ligands for these chemokine receptors were quantified in plasma (Luminex). Total, integrated and ZTLR circle HIV DNA and cell counts were determined (CA-US) HIV RNA was quantified in CD4+ T-cells. Spearman correlations and negative binomial regression models were performed to test associations between markers of virus persistence and CR expression on CD4+ T-cells adjusting for current and nadir CD4 T-cell counts.

Results: Subjects were predominantly male (96%) with a median CD4+ 624 (IQR:533-859) cells/μL. There were statistically significant negative correlations between current CD4 count and expression of the inflammatory CR CXR5 (r=−0.53, p<0.001), CXCR3 (r=−0.57, p<0.001) and a positive correlation with the homeostatic CR CCR7 (r=0.59, p<0.001). There was a statistically significant negative correlation between integrated HIV DNA and current CD4 (r=−0.52, p<0.001) but not nadir CD4. CXR5 was the only CR that substantially correlated positively with integrated HIV RNA (r=0.29, p=0.045) but this largely disappeared when controlled for current or nadir CD4. In a negative binomial regression model, 2-LTR circles were negatively correlated with nadir CD4 (r=−0.45, p=0.002) but not current CD4. In a negative binomial regression model, ZTLR circles were positively correlated with CXCR3 expression (r=0.001) and CXCR5 expression (r=0.032) and both remained statistically significant after adjusting for nadir or current CD4 count. There was no significant relationship between total HIV DNA, CA-US RNA and CR expression. There was no statistically significant relationship between virus persistence and any of the chemokines measured in plasma, except for a positive correlation between 2-LTR circles and the ligand for CXCR7, CCL21 (r=0.30, p=0.045).

Conclusions: The association of ZTLR circles with nadir CXR5 and CXCR3 and CXCR5 expression on CD4+ T-cells raises the possibility of ongoing replication in cells that express these specific inflammatory CRs, such as effector memory T-cells, particularly in individuals who initiate ART at lower CD4 counts.

Background

Integrated T-cell recruitment and expression of both homeostatic chemokine receptors and inflammatory chemokine receptors are preferentially targeted by the virus, and levels of these receptors reflect the size of the HIV latent reservoir. Therefore, assessments of these receptors on CD4+ T-cells may provide new insight into the size of the latent reservoir.

Methods

(1) Current CD4+ T-cell count and expression of homeostatic and inflammatory chemokine receptors are strongly associated.

Conclusions

(4) In multivariate models, adjusting for current and nadir CD4+ T-cell counts, CXCR3 and CXCR5 are associated with 2-LTR circles.

(5) Integrated HIV DNA is enriched in central memory CD4+ T-cells that express CXCR6 and CXCR3.

(6) Summary

1. There is a strong association between current CD4 and expression of both homeostatic and inflammatory chemokine receptors as well as the size of the reservoir as measured by in situ TUNEL

2. The current association between nadir CD4 and 2-LTR circles suggests that persistent virus replication may be greatest in those who initiate ART late.

3. Multivariate analysis adjusting for current and nadir CD4 showed that CXCR3 and CCR5 were associated with 2-LTR expression

4. CM cells that express CXCR3 and CXCR6 were enriched for integrated DNA

Conclusions

(2) Current and nadir CD4+ T-cell integrated DNA and 2-LTR circles are inversely correlated with integrated HIV RNA

(3) CXCR3 is associated with integrated HIV DNA.

Committee: T-cell expression and 2-LTR circles in patients on antiretroviral therapy

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Table 3: Correlations between HIV reservoir markers and current and nadir CD4+ T-cell count.

Table 4: Correlations between chemokine receptor expression and current and nadir CD4+ T-cell count.

(1) Current CD4+ T-cell count and expression of homeostatic and inflammatory chemokine receptors are strongly associated.

(2) Current and nadir CD4+ T-cell integrated DNA and 2-LTR circles are inversely correlated with integrated HIV RNA

(3) CXCR3 is associated with integrated HIV DNA.

Table 5: Negative binomials regression models show that CCR5 is a strong predictor which correlates significantly with integrated HIV DNA as a percentage chemokine receptor expression on total CD4+ cells. (A) Adjusted for effect of current and nadir CD4 T-cell counts. (B) Adjusted for the effect of antiretroviral therapy (ART) and current and nadir CD4 T-cell counts. Persistence of ZTLR circles and other HIV DNA markers were not statistically significant and CCR5-integrated HIV DNA was the only marker that is statistically significant in the multivariate model after controlling for sections of the reservoir as measured by in situ TUNEL

2. The current association between nadir CD4 and 2-LTR circles suggests that persistent virus replication may be greatest in those who initiate ART late.

3. Multivariate analysis adjusting for current and nadir CD4 showed that CXCR3 and CCR5 were associated with 2-LTR expression

4. CM cells that express CXCR3 and CXCR6 were enriched for integrated DNA