CD4+ and CD8+ T Cell Activation Are Strongly Associated With HIV-1 DNA in Resting CD4+ T Cells

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Background: The association between the host immune environment and the size and between multiple measurements of the reservoir (Eriksson et al, PLoS Path 2013). Here, we explored the association between HIV persistence as defined by these assays and the level of T cell activation and function.

Methodology: We performed multiple simultaneous measurements of HIV persistence and analyzed their association with immune function and T cell activation in 30 antiretroviral-treated adults: 10 who started therapy during acute infection and 20 who initiated treatment during chronic infection. All individuals were on a suppressive antiretroviral regimen for at least 36 months and had > 350 CD4 cells/ul. The following assays were performed on patient samples: viral outgrowth, digital droplet PCR (ddPCR) for HIV-1 DNA and 2-LTR circles in PBMCs and resting CD4+ T cells, Alu PCR for integrated HIV-1, and a single copy assay for plasma virus. Flow cytometry was performed to measure frequencies of activated and HIV-specific T cells in blood. Spearman rank correlation coefficients were calculated.

Results: The most consistent host response associated with HIV persistence was frequency of “activated” (%HLA-DR+ +/- CD38+) CD4+ and CD8+ T cells. CD4+HLA-DR+ T cells were strongly associated with frequency of resting CD4+ cells containing total HIV-1 DNA as measured by ddPCR (ρ = 0.65, P=0.006). There were similar associations with activated CD8+ T cells (% CD4+HLA-DR+CD38+: ρ = 0.51, P=0.04). This association was strongest with activation in central memory and effector memory CD4+ T cells. Other markers of activation including PD-1 and the co-expression of all markers (CD38+HLA-DR+CCR5+PD1+) on CD8+ T cells were also correlated with HIV DNA in resting CD4+ T cells (PD-1: ρ = 0.37, P=0.04). HIV-specific CD4+ T cells expressing TNF-α and IL-21 were positively correlated with total HIV DNA in resting cells by ddPCR (TNF-α: ρ = 0.54, P=0.01, IL-21: ρ = 0.72, P=0.004). Similar non-significant trends were observed with HIV specific CD4+ T cells expressing IL-2 and IFN-γ. Non-significant negative associations were observed between HIV-specific CD4+ T cells and the frequency of latently infected cells by co-culture.

Conclusions: The frequency of CD4+ and CD8+ T cells expressing activation markers and the frequency of HIV-specific CD4+ cells are directly associated with the frequency of resting cells harboring HIV DNA. Although defining causation in this study is not possible, one possibility is that T cell activation drives persistence, perhaps as a consequence of cell proliferation. This may have implications for reactivation strategies, as reversal of latency, in the absence of effective killing and complete suppression of viral replication, could lead to an increase in reservoir size.