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Increased frequency of cytotoxic CXCR5 + effector memory CD8 + T cells during natural control of HIV-1 infection

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Purpose: Potent HIV-specific immune responses and a small latent viral reservoir are likely required to control viral replication during HIV-1 infection. Here we investigated the antiviral CD8 + T cell response of elite and viremic controllers (EC and VC) and antiretroviral therapy-(ART) suppressed patients at baseline and after peptide stimulation.

Method: Peripheral blood mononuclear cells of 58 patients were analyzed by 18 color flow cytometry and IFN-γ ELIspot at baseline and after 7 days of in vitro HIV peptide stimulation (PTE GAG pool, NIH). Plasmas were analyzed for IFN-γ, CXCL-10, IL1-β, IL6, TNF-a, IL-18 concentrations. Cytometry data was clustered using viSNE and analyzed by Boolean gating strategy to assess multifunctional characteristics. Statistical comparison was executed with QluCore and Prism nonparametric statistics (Kruskal-Wallis test correcting for multiple comparison).

Results: IL-18 in plasma and CD38 expression on CD4 + T cells were significantly lower in EC and ART patients with low reservoir than in VC ($p<0.05$). We observed a significant increase in IFN-γ production at baseline and after 7 days of peptide stimulation ($p<0.0005$) while CD107a and Ki67 expression were also significantly increased for ECs compared to ART patients ($p<0.001$).

Detailed phenotyping revealed that CD8 + effector memory T cells which are IFN-γ^+, Ki67$^+$, CD107a^{bright}, Perforin^{bright} and GrzB$^+$ significantly increased in EC ($p<0.005$) as compared to VC and ART patients. Similarly we observed central memory CD8 + T cells subsets with increased cytotoxic and polyfunctional features in EC ($p<0.005$). Interestingly, CD8 + T cells subsets expressing CXCR5, a homing receptor for lymph node follicles, and cytotoxic markers were significantly increased in EC as well ($p<0.005$).

Conclusion: Distinct functional subsets coexist during natural control of HIV-1 infection. Access to the B cell zone of lymph node follicles by cytotoxic CD8 + T cells might explain long-term control of the HIV reservoir.