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Type-1 programmed dendritic cells induce primary CTL capable of effectively targeting the HIV-1 reservoir

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Background: The "kick and kill" strategy for the cure of chronic HIV-1 infection involves unmasking cells harboring the latent viral reservoir followed by their immune elimination. We hypothesize that a broad priming of de novo rather than memory HIV-1 specific CTL will be required to effectively target the autologous HIV-1 reservoir, and that this "kill" can be best achieved using specifically programmed type-1 dendritic cells (DC1).

Methods: Mature, IL-12p70 producing DC1 were generated using a combination of either TNFa, IL-1b, poly IC, IFNa and IFNg, or CD40L and IFNg. Mature, IL-12 deficient DC were generated using either a combination of TNFa, IL-1b, IL-6 and PGE2, or CD40L alone. CD8+ T cells were purified from HIV-1 negative donors, and both naive (primary) and memory CD8+ T cells were isolated from HIV-1 infected Multicenter AIDS Cohort Study participants who were on virus-suppressive cART for several years. These cells were stimulated with autologous DC loaded with HIV-1 Gag peptides or autologous AT2-inactivated HIV-1. Resulting CTL activity was assessed by IFNg ELISPOT and antiviral cytotoxicity assays targeting autologous HIV-1 infected CD4+ T cells.

Results: DC1 proved far superior to the IL-12-deficient DC for inducing primary CTL responses in both infected and uninfected donors. Importantly, DC1 required CD40L "help" at the onset of priming cultures for successful CTL induction and expansion. Both primary and memory CTL each responded to distinct autologous HIV-1 Gag peptides with robust IFNγ production. However, a broader targeting of known MHC class I-restricted epitopes was achieved by the primary CTL responders than the memory cells. Importantly, despite substantial IFNγ production by both T cell subsets, the primary CD8+ T cells were significantly superior to restimulated memory T cells in eradicated HIV-1 infected CD4+ T cells in the CTL assays.

Conclusions: We demonstrate that naïve T cells from HIV-1 infected persons on cART have the repertoire and ability to be primed by high IL-12p70-producing DC1 to effectively target the HIV-1 reservoir, while memory CTL responses are suboptimal. These findings highlight the importance of directing HIV-1 curative strategies towards the induction of de novo rather than memory HIV-1-specific CTL responses.

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