Proliferation of CD4+ T Cells Containing Replication-Competent HIV-1

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Background and Introduction

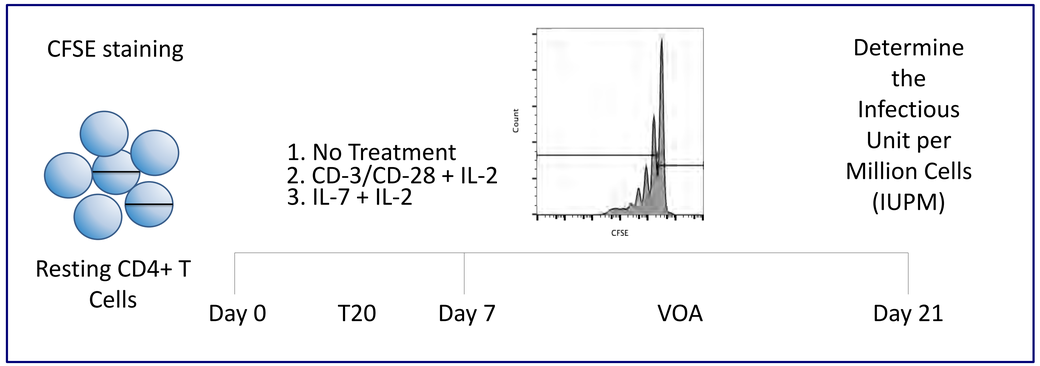
Background. Persistence of the human immunodeficiency virus type-1 (HIV-1) in a latent form in resting memory CD4+ T cells remains the major barrier to curing HIV-1 infection. Previous studies have shown that HIV-infected CD4+ T cells can clonally expand (1). However, it remains unclear what mechanism drives the expansion of HIV-infected CD4+ T cells and whether HIV-1 proviruses in these clonally expanded populations are replication competent. We hypothesize that clonal expansion of HIV-1-infected CD4+ T cells is caused by physiologic stimulations including antigen-induced T cell activation and homeostatic proliferation. Some clonally expanded CD4+ T cells can potentially produce replication-competent virus.

Introduction. Interleukin 7 (IL-7) and interleukin 2 (IL-2) have been demonstrated to play a central role in the development and homeostasis of T cells. A previous study has suggested that infected central memory cells can proliferate in response to IL-7 and IL-2 (2). It is unknown whether CD4+ T cells harboring replication-competent provirus can proliferate when they encounter IL-7 and IL-2.

Methods

Resting CD4+ T cells from aviremic patients under suppressive antiretroviral therapy were labeled with carboxyfluorescein succinimidyl ester (CFSE) and treated with CD3/CD28 costimulation or IL-7/IL-2 in the presence of enfuvirtide(T20) to prevent new rounds of infection. After 7 days of culture, CD4+ T cells were sorted based on CFSE dilution and plated in a viral outgrowth assay (VOA) to quantify infectious HIV-1 in both non-proliferated and proliferated populations. Cells that have proliferated with IL-7/IL-2 treatment were tested in viral outgrowth assay with or without PHA activation to determine whether IL-7/IL-2 can induce cell proliferation and reactivate HIV without additional PHA stimulation.

Resting CD4+ T cells were also sorted based on expression of CD45RA, CCR7 and CD27 into naïve, central memory, transitional memory and effector memory CD4+ T cells. All the subsets of CD4+ T cells were treated with IL-7/IL-2 to test if all subsets are able to proliferate as it has been demonstrated that all CD4+ T cell subsets harbor detectable amount of HIV DNA (3).



Results

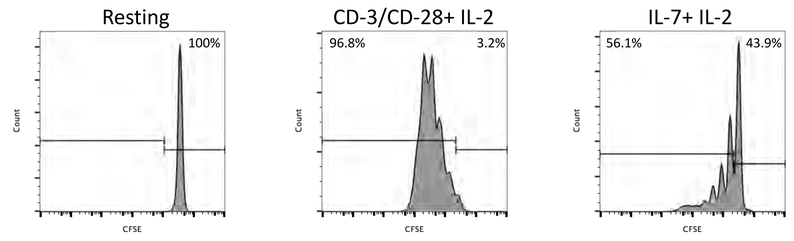


Figure 1. Proliferation of CD4+ T cells upon treatment with CD-3/CD-28+ IL-2 or IL-7+ IL-2 treatment.

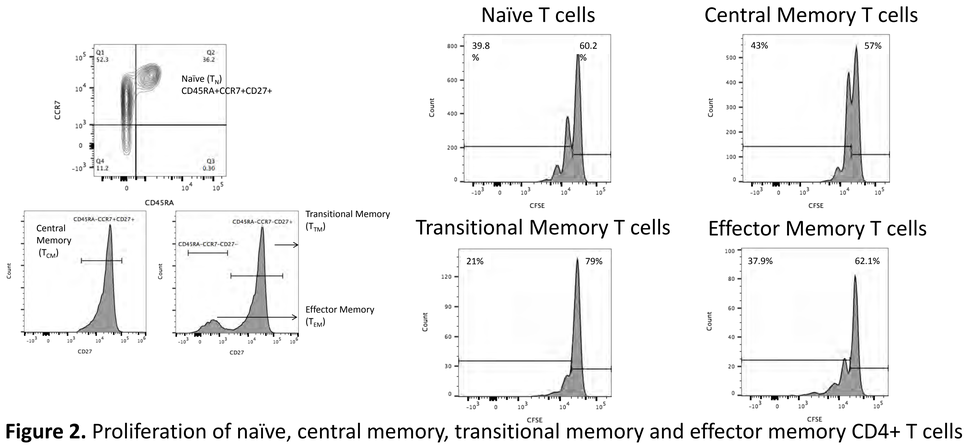


Figure 2. Proliferation of naïve, central memory, transitional memory and effector memory CD4+ T cells upon IL-7/IL-2 treatment.

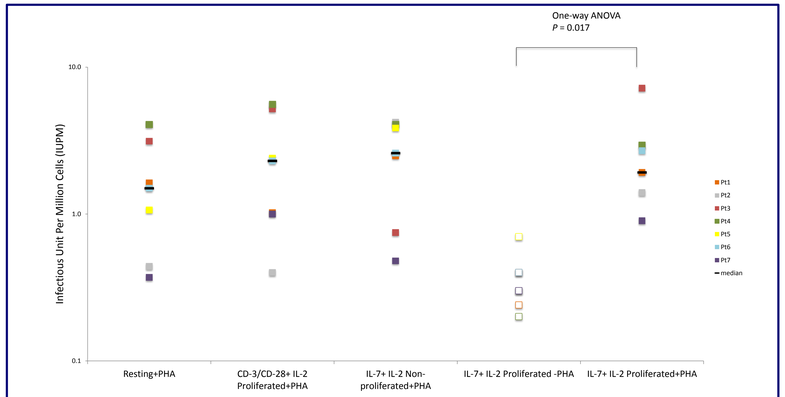


Figure 3. Infectious unit per million cells measurement in non-proliferated and proliferated populations upon CD-3/CD-28+ IL-2 or IL-7+ IL-2 treatments.

Conclusions

Our results demonstrated that CD4+ T cells containing replication-competent virus are able to proliferate in response to T cell activation or cytokine treatment. However, no viral outgrowth is observed from cells that have proliferated with IL-7/IL-2 without additional PHA stimulation, suggesting provirus in the CD4+ T cells that proliferate in response to cytokines are not reactivated.

References

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Acknowledgements

This work was supported by the Bill and Melinda Gates Foundation, the Howard Hughes Medical Institute, the W.W. Smith Chartable Trust AIDS Research Grant, and also by the following NIH grants; University of North Carolina - 5-31558, NIAIDR37AI051178, and by three Martin Delaney Collaboratory Grants: 1) Harvard/Beth Israel –BIDMC: UM1AI126603 2) Wistar Institute – BEAT-HIV: UM1AI126620 and 3) University of San Francisco- DARE: UM1AI126611.