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Targeting HIV-1 persistence in CD4 T memory stem cells by pharmaceutical inhibition of beta-catenin

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Background: Treatment with antiretroviral combination therapy can effectively suppress active HIV-1 replication, but HIV-1 persists in the human body and rapidly rebounds after discontinuation of therapy. T memory stem cells (Tscm) represent a recently-discovered subpopulation of T cells that persist for extremely long periods of time and are maintained by a stem cell-like developmental program governed through the wnt/beta-catenin pathway. The role of CD4 Tscm for viral persistence is unclear.

Methods: PCR assays were used to determine the amount of cell-associated HIV-1 DNA in sorted CD4 T cell subsets from HAART-treated HIV-1 patients. The presence of replication competent virus within the CD4 T cell subsets was tested using viral reactivation assays. Phylogenetic association studies were performed with viral Env sequences amplified form plasma and individuals CD4 T cell subsets. Effects of the pharmaceutical beta-catenin inhibitor C-82, (the active metabolite of PRI-724, currently tested in clinical trials, e. g. NCT01606579) on CD4 T cell differentiation were studied using ex-vivo culture assays.

Results: HIV-1 DNA in CD4 Tscm from HAART-treated patients were high and exceeded HIV-1 DNA levels in alternative cell subsets. Viral reactivation assays demonstrated that CD4 Tscm harbor replication-competent virus. Viral sequencing studies revealed close phylogenetic associations between circulating plasma HIV-1 strains during early disease stages, and HIV-1 DNA isolated from CD4 Tscm after 6-12 years of therapy, consistent with long-term viral persistence in CD4 Tscm. In vitro culture assays demonstrated that pharmaceutical beta-catenin inhibitors can promote differentiation of CD4 Tscm into more short-lived effector CD4 T cells.

Conclusion: Tscm serve as a long-lasting reservoir for HIV-1 that importantly contributes to viral persistence. Targeting this specific cell compartment by pharmaceutical beta-catenin inhibitors may have an adjunct or additive role for reducing long-term viral persistence in CD4 Tscm.