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Dasatinib preserves SAMHDI antiviral activity in CD4+ T-cells treated with IL-7

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Background: HIV-1 post-integration latency in quiescent CD4+ T cells is responsible for viral persistence despite antiretroviral treatment. It was proposed that the increase in proviral load in HIV-infected patients after IL-7 treatment was due to homeostatic proliferation of memory CD4+ T cells. We determined previously that IL-7 increased HIV-1 infection through phosphorylation and subsequent inactivation of the restriction factor SAMHDI. Now we analysed SAMHDI phosphorylation in PBMC from patients enrolled in ACTG 5214 study (NTC00099671), in order to elucidate the role of IL-7 in HIV-1 proviral integration and persistence and whether this could be related to SAMHDI inactivation. In addition, we determined that the tyrosine-kinase inhibitor Dasatinib preserved SAMHDI antiviral activity, avoiding IL-7-mediated HIV-1 infection.

Methods: PBMC samples obtained from 10 patients enrolled in ACTG 5214 study (NTC00099671), collected before (day 0) and 4 after administration of IL-7. PBMCs obtained from 2 patients diagnosed with chronic myeloid leukemia (CML), on chronic treatment with Dasatinib. Resting CD4+ T cells from healthy donors obtained by negative selection from PBMCs. Phosphorylation of SAMHDI at T592 was determined by immunoblotting and flow cytometry. Proviral integration was analyzed by TaqMan qPCR. Dasatinib (BMS-354825, Sprycel) was provided by Bristol-Meyers Squibb.

Results: 1) IL-7 (1nM) induced SAMHDI phosphorylation, interfering with its antiviral activity. 2) IL-7-mediated SAMHDI phosphorylation greatly increased HIV-1 infection in purified CD4+ T cells, increasing early and late retrotranscription, as well as proviral integration. 3) A significant increase in pSAMHDI was observed in central memory CD4+ T cells from HIV-infected patients treated with IL-7 (ACTG 5214). 4) Dasatinib completely inhibited SAMHDI phosphorylation at 75nM, interfering with HIV-1 retrotranscription and consequently, with proviral integration. 5) CD4+ T cells from patients with CML treated with Dasatinib showed lower expression of SAMHDI phosphorylated.

Conclusions: By inducing SAMHDI phosphorylation, IL-7 increases susceptibility of resting CD4+ T lymphocytes to infection, leading to HIV persistence. SAMHDI regulation plays a central role in the establishment of HIV-1 reservoirs and represents a major target for therapeutic intervention. Dasatinib is the first compound currently used in clinic that has been described to preserve the antiviral function of an innate factor such as SAMHDI.