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Dictating SAMHD1 in CD4+ T lymphocytes and monocytes by immune activation during chronic HIV-1 infection

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SAMHD1 restricts human immunodeficiency virus type 1 (HIV-1) replication in myeloid cells and CD4+ T cells. The relevance of SAMHD1 in HIV-1 pathogenesis in vivo remains unclear. Flow cytometric analysis was used to directly visualize ex vivo and after in vitro SIV-Vpx treatment, SAMHD1 expression in CD4+ T cells and monocytes. Here, we report that aberrant SAMHD1 was found in HIV-1 target cells from chronically HIV-1 infected individuals in relation to HIV pathology and lose control of viremia. During chronic HIV-1 infection, activated CD4+ T cells without SAMHD1 expression were severely reduced. In a proportion of activated CD4+ T cells, SAMHD1 became susceptible to SIV-Vpx mediated degradation, which was absent from uninfected donors. The frequency of monocytes susceptible to degradation was less than that of uninfected donors and was inversely correlated with plasma HIV-1 viral load. These alterations were linked to HIV-1 pathology and were irreversible, even after long-term fully suppressive antiretroviral treatment. In vitro assays further revealed that T-cell activation and an upregulated IFN-I pathway contributed to these altered SAMHD1 properties. These findings provide insight into how immune activation during HIV-1 infection leads to irreparable aberrations in restriction factors and in subsequent viral evasion from host antiviral defenses.

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