

Oral Abstract Session I: Pathways to establishing and maintaining HIV latency

OAI-I

CTLA-4-expressing memory CD4+ T-cells are critical contributors to SIV viral persistence

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Background: Understanding the immunophenotype and anatomic location of latently infected cells represents a critical challenge in designing a cure for HIV. Among memory CD4+ T-cells, those expressing co-inhibitory receptors (Co-IRs) are strong candidates for being enriched in latent HIV, given their negative regulatory function and upregulation on T-cells following HIV infection. However, little is known regarding the dynamics of T-cells expressing multiple Co-IRs following suppressive ART and their contribution to the HIV/SIV reservoir, particularly in tissues.

Methods: We investigated the relationship between the level of Co-IR expression on memory CD4+ T-cells and their level of latent virus in 10 ART-treated, SIV-infected rhesus macaques (RMs). RMs initiated a 5-drug ART regimen 6-8 weeks after SIVmac251 infection, which was maintained until plasma viremia was < 60 copies/mL for at least 3 months. Blood and tissue levels of memory CD4+ T-cells expressing multiple Co-IR (PD-1, CTLA-4, TIM-3, 2B4, TIGIT) were longitudinally analyzed by flow cytometry. Memory CD4+Co-IR+ subsets were sorted twice during viral suppression based on their expression of PD-1, CTLA-4, and TIM-3, to quantify levels of cell-associated SIV-DNA and RNA.

Results: The majority of memory CD4+ T-cells from the blood, GI tract, lymph node, and spleen expressed multiple Co-IRs, specifically PD-1 and CTLA-4, and their frequencies remained stable or increased during SIV infection, even with suppressive ART. Following 1 month of viral suppression, both memory CTLA-4+(PD-1-) and PD-1+(CTLA-4-) CD4+ T-cells harbored significantly higher levels of SIV-DNA in the LN. Yet, after 3 months of suppression, only CTLA-4+ CD4+ T-cells, in the absence of other Co-IRs, were significantly enriched in SIV-DNA in the PBMCs, compared to Co-IR(-) cells, and in the LN, demonstrating the specific persistence of this virally infected subset. Furthermore, this subset did not express high levels of SIV-RNA, which suggests that these CTLA-4+ cells likely harbor latent SIV.

Conclusions: Despite comprising a small frequency of memory CD4+ T-cells, CTLA-4+ T-cells represent a novel subset of virally enriched cells that may critically contribute to persistence in ART-suppressed individuals. These findings highlight the benefit of therapeutically blocking both CTLA-4 and PD-1 to target a large fraction of the HIV reservoir.