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## SEVERE MUCOSAL DEPLETION OF CD4<sup>+</sup> T CELLS IN ABSENCE OF GENERALIZED IMMUNE ACTIVATION DURING NON-PATHOGENIC SIV-INFECTED SOOTY MANGABEYS

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**BACKGROUND:** In contrast to HIV infection of humans and simian immunodeficiency virus (SIV) infection of macaques, the natural SIV infection of sooty mangabeys is not associated with an AIDS-like disease, despite high levels of viral replication. Recent studies indicate that virus-mediated CD4<sup>+</sup> T cell depletion in mucosal associated lymphoid tissue (MALT) plays a key role in the pathogenesis of AIDS. The aim of this study was to characterize the immunological features of non-pathogenic SIV infection of sooty mangabeys in the MALT.

**METHODS:** We included 18 naturally SIV-infected and 10 uninfected sooty mangabeys in a cross-sectional and longitudinal analysis of T cells derived from MALT (rectal biopsy and broncho-alveolar lavage), lymph nodes, and peripheral blood. The level of T cell activation (HLA-DR, CD69, loss of CD127), proliferation (Ki67), and CCR5 expression was measured by flow cytometry. Naïve and memory T cells were defined based on the expression of CD28 and CD95. Viremia was measured by real-time polymerase chain reaction. We treated 6 animals with the antiretroviral drugs tenofovir and emtricitabine for 6 weeks.

**RESULTS:** In both SIV-infected and uninfected sooty mangabeys, the majority of mucosal T cells display a memory or effector phenotype (i.e., CD95<sup>+</sup>), with a small fraction of CD4<sup>+</sup>CCR5<sup>+</sup> T cells regardless of SIV infection. In uninfected sooty mangabeys, the percentage of CD4<sup>+</sup> T cells is similar in peripheral blood, lymph nodes, and MALT. In contrast, SIV-infected sooty mangabeys show a significant depletion of CD4<sup>+</sup> T cells isolated from both rectal biopsy and broncho-alveolar lavage, with 2 animals maintaining <1% of residual CD4<sup>+</sup> T cells in the MALT. A significant increase

in mucosal CD4<sup>+</sup> T cells was observed in 3 of the 6 SIV-infected sooty mangabeys after treatment with tenofovir and emtricitabine. Interestingly, SIV-infected sooty mangabeys show levels of mucosal immune activation (measured as percentage of activated or proliferating T cells and effector T cells in the MALT) that are similar to those of uninfected animals. In SIV-infected sooty mangabeys, however, an inverse correlation was found between the percentage of MALT-associated CD4<sup>+</sup> T cells and the overall level of mucosal immune activation.

**CONCLUSIONS:** Natural, non-pathogenic SIV infection of sooty mangabeys is characterized by a significant depletion of CD4<sup>+</sup> T cells in the MALT in the context of normal peripheral blood CD4<sup>+</sup> T cell counts and the absence of generalized immune activation. These results suggest that the clinical onset of AIDS may require both the depletion of MALT-associated CD4<sup>+</sup> T cells and the presence of significant mucosal or systemic immune activation.

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