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AIDS-DEFINING CD4 T-CELL LEVELS CORRELATE WITH EXPANDED CO-RECEPTOR USAGE DURING NONPATHOGENIC SIV_{SM} INFECTION OF SOOTY MANGABEYS

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BACKGROUND: Simian immunodeficiency virus (SIV) infection of its natural hosts, such as sooty mangabeys, results in high viral loads in the absence of immune dysfunction and clinical AIDS. However, cross-species transmission of SIV to non-natural hosts (HIV in humans; SIV in macaques) generally results in high viral loads, CD4 decline, and clinical AIDS. Here, identification of sooty mangabeys with CD4 T cells <100/mL blood represent a novel model to study SIV immunopathogenesis.

METHODS: We inoculated 6 sooty mangabeys intravenously with plasma from a naturally infected sooty mangabey and followed them for viral and immunologic parameters. Flow cytometric analysis was used to assess CD4 levels and T cell proliferation / activation / apoptosis markers (Ki67, CD69, HLA-DR, CD28, CD95, annexin V). Viral co-receptor usage was assessed by a cell:cell fusion assay and confirmed by sequence analysis.

RESULTS: Two SIV_{sm}-inoculated sooty mangabeys exhibited AIDS-defining CD4 T cell levels at 47 (SM1) and 79 (SM2) weeks post-infection. CD4 T cells were significantly reduced from all immunologic compartments assessed including peripheral blood mononuclear cells, lymph nodes, and gut-associated lymphoid tissue. Interestingly, no correlation was observed between decreased CD4 T-cell levels and increased levels of proliferation, activation, or apoptosis. Assessment of co-receptor usage at 4 weeks post-infection indicated that all 6 sooty mangabeys were infected with CCR5 tropic virus. However, after the CD4^{low} phenotype was observed, the Env had changed such that it was now capable of utilizing CXCR4 in addition to CCR5. Sequence analysis revealed an increase in basic amino acids in the V3 loop of Env associated with expanded co-receptor

usage (similar to HIV+ patients). Surprisingly, the CD4^{low} phenotype has not resulted in clinical AIDS despite >4 years at <100 CD4 cells/mL blood. In addition, AIDS-defining CD4 levels have been observed in 3 naturally infected sooty mangabeys at the Yerkes Primate Center, indicating that this finding was not due to the intravenous inoculation route utilized in SM1 and SM2.

CONCLUSIONS: These data indicate that expanded co-receptor usage can occur in SIV-infected sooty mangabeys. Moreover, CD4 levels <100/mL blood are likely sustained by direct viral killing of T-cell targets; bystander-associated cell death does not appear to play a major role. The CD4^{low} sooty mangabeys provide evidence that AIDS-defining CD4 levels and progression to clinical AIDS can be separated; increased immune activation that occurs in HIV⁺ humans, but not in sooty mangabeys, appears to be crucial for progression to AIDS.

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