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Nef-mediated TCR-CD3 and MHC-I down-modulation prevents CD4+ T cell depletion in natural SIV infection

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High level immune activation and apoptosis represent a hallmark of HIV-1 infection that is absent from non-pathogenic SIV infections. Recently, we reported that nef alleles from most primate lentiviruses, including HIV-2, down-modulate TCR-CD3 from HIV- or SIV-infected human and sooty mangabey T-cells, thereby blocking their responsiveness to activation (Cell 2006, 125:1055). In contrast, nef alleles from HIV-1 and a subset of closely related SIVs fail to down-regulate TCR-CD3 and to inhibit activation-induced cell death. Thus, differences in Nef function likely provide a mechanism for the varying levels of immune activation observed in pathogenic and nonpathogenic primate lentiviral infections. To further assess the role Nef function in vivo we functionally characterized nef alleles derived from 11 SIVsmm-infected mangabeys with >500 CD4+ T-cells/µl and from 15 animals showing a substantial loss of CD4+ T-cells. Our results showed that nef alleles from sooty mangabeys with low CD4+ T cells counts exhibited significantly reduced activity in TCR-CD3 and class I MHC (MHC-I) down-modulation, compared to those derived from animals with normal CD4+T counts. Thus, our data strongly suggest that the ability of Nef (i) to down-modulate TCR-CD3 and to prevent programmed cell death and (ii) to down-regulate MHC-I to reduce CTL lysis of virally infected CD4+ T cells helps the natural hosts of SIV infection to maintain normal CD4+ T cell counts despite high levels of viral replication.