Retrovirology

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Oral presentation

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 non-pathogenic primate lentiviral infections. To further assess the role Nef funtion 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.