A COMPARISON OF PATHOLOGICAL CORRELATES OF TWO ATTENUATED MUTANTS OF HIGHLY PATHOGENIC SIVmac239.


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A key feature of SIV and HIV infection is the rapid and near complete depletion of mucosal CD4+ T cells; however, this depletion also occurs in nonpathogenic infections (e.g. SIVagm infection of African green monkeys and SIVsmm infection of sooty mangabeys) suggesting that it is a common feature of primate lentiviral infections. Here we evaluate CD4+ T cell depletion in the mucosa of Indian origin rhesus macaques for two variants of highly pathogenic SIVmac239; Δnef and ΔGY. Compared to the parental SIVmac239, Δnef has a deleted nef gene, critical for virulence in vivo; ΔGY has two amino acids (Gly-720 and Tyr-721) deleted from a GYxxØ trafficking motif in the envelope (Env) cytoplasmic tail. In contrast to SIVmac239 infection, acute infection with ΔGY or Δnef spared gut CD4+ T cells (<10% reduction) despite high plasma viral loads, particularly for ΔGY (average peak 1.31 x 10^7 copies/ml). Whereas SIVmac239 is usually found in immune effector and immune inductive sites, ΔGY, was limited to immune inductive sites (organized lymphoid nodules and germinal centers) of the intestine and peripheral lymphoid organs. Confocal microscopy consistently identified ΔGY-infected cells as CD3+ T cells; ΔGY was not observed in macrophages or the brain, indicating a less diverse target cell population and tissue distribution than for SIVmac239. Over time the ΔGY-infected animals with the highest viral loads exhibited a slow decline in gut CD4+ cells. Thus, for both ΔGY and Δnef a striking reduction in the ability to deplete mucosal CD4+ T cells was seen, suggesting a common defect in entering and/or replicating at this site. Whether these viruses become increasingly pathogenic over time is currently under investigation.

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