HIV-1 gp120 Binding to DC-SIGN Sensitises Dendritic Cells for Killing by Multiple Stimuli

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HIV-1 envelope protein gp120 can bind to DC-SIGN expressed by dendritic cells (DC) that subsequently transfer infectious virus from peripheral sites to secondary lymphoid tissues. HIV-1(+) sera can contain high levels of circulating envelope protein. We show that recombinant gp120, and circulating envelope protein in serum, primes DC to undergo CD40-mediated apoptosis on co-culture with activated CD4 T cells or CD40 ligand transfectants. This pathway is, at least in part, mediated through gp120 binding to DC-SIGN, and is accompanied by down-regulation of the anti-apoptotic proteins Bc12, Bclx/L and phosphorylated Akt. Live HIV-1 virus propagated *in vitro* also primes DC to undergo apoptosis on co-culture with CD40L transfectants. However when live virus-pulsed DC are co-cultured with activated CD4 T cells, the DC are not killed and virus is transmitted to the T cells for replication. Both recombinant gp120 and circulating envelope protein in HIV-1 serum can also sensitize DC for apoptosis after exposure to LPS or the inflammatory cytokines TNF-α and IL1-β. Our observations suggest that circulating envelope protein and soluble gp120 binding to DC-SIGN may result in death of DC, and depression of T cell responses, during disease progression to AIDS.