Retrovirology

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Oral presentation

HIV-1 pathogenesis: IFN-alpha-dependent and -independent mechanisms of T cell death and unresponsiveness

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Functional unresponsiveness and numerical depletion of CD4+ T cells are immunologic characteristics of HIV-1 disease progression. Analyses of these poorly-understood phenomena by our laboratory indicate that both infections and noninfectious HIV-1 bind to and activate CD4+ plasmacytoid dendritic cells (pDC) to express: (1) interferon-alpha (IFN-alpha); and (2) indoleamine 2,3-dioxygenase (IDO). We found that HIV-induced IFN-alpha bound its receptor INFAR2 on CD4+ T cells, inducing expression of the death molecule TNF-Related Apoptosis-Inducing Ligand (TRAIL) by CD4+ T cells. The binding of infectious or noninfectious HIV-1 to CD4+ T cells induced expression of the TRAIL death receptor DR5, resulting in selective apoptosis of CD4+ T cells. IDO is a tryptophan-catabolizing enzyme that depletes T cells of tryptophan, resulting in their unresponsiveness. We found that HIV-induced expression of IDO by pDC activated the GCN2 stress response kinase in T cells, resulting in inhibition of both CD4+ and CD8+ T cell function. This effect of IDO on both T cell subsets contrasts with expression of TRAIL and DR5, which is limited to CD4+ T cells and their death. Anti-IFN-alpha antibody blocked IFN-alpha production by pDC and TRAIL expression by CD4+ T cells, but not expression of IDO by pDC. Blocking of HIV-1 binding to CD4 on pDC inhibited their expression of both IFN-alpha and IDO. Our comparative analyses reveal similarities and differences in HIV-induced mechanisms that contribute to T cell death and unresponsiveness.