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Oral presentation

Mutational analysis of HIV-1 gp41 mediated apoptosis and its correlation with fusion/hemifusion

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The loss of CD4+ T cells in HIV-1 infections is hypothesized to be caused by apoptosis of bystander cells mediated via HIV-1 Env glycoprotein. However, the mechanism via which Env mediates this process remains controversial. Specifically the role of HIV-1 gp120 binding to CD4 and CXCR4 versus the fusion process mediated by gp41 remains unresolved. Previously we have demonstrated that Env induced apoptosis in bystander cells is gp41 dependent and correlates with the redistribution of membrane lipids between Env-expressing cells and target cells (hemifusion). We further examined the role of HIV-1 gp41 by performing mutational analysis of HIV-1LAI gp41 mediated apoptosis in bystander cells. A mutation in the fusion domain of gp41 (V513E) resulted in a fusion defective Env that failed to induce apoptosis. Altering fusion capacity of Env via N terminal helix mutation (G547D) or deletion of the cytoplasmic tail (CtDel) of gp41 resulted in reduced and enhanced cell to cell fusion respectively and correlated with apoptosis. Interestingly, mutation in the loop region of gp41 (D589L) exhibited a hemifusion restricted phenotype that induced bystander cell death while being a weak mediator of both cell to cell and virus to cell fusion. However, D589L Env did transfer the lipid dye DiI to the apoptotic bystander cells confirming its ability to induce apoptosis via hemifusion. Hence, we provide the first direct evidence that gp41 mediated hemifusion is sufficient for induction of apoptosis in bystander cells and may explain the mechanism of HIV-1 Env induced T cell depletion.