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Proteasome-independent restriction of HIV-1 infection in human placental trophoblast cells

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Résumé:

Background: Human trophoblast cells, which form the outer barrier of the placenta, are resistant to cell-free HIV-1 infection. These cells play an important role in limiting in utero mother-to-child transmission; although it is known that the restriction can be overcome by VSV-G HIV-1 pseudotypes, the precise mechanisms of the restriction remain unclear. Evidence suggests that certain restriction factors may limit HIV-1 infection by channeling incoming virions towards the proteasome, where degradation occurs. We therefore hypothesized that restriction of HIV-1 infection in trophoblasts could be due to proteasomal-degradation of incoming virus.

Methods: The human choriocarcinoma cell-line, BeWo (CD4- and CD4+), was used in the study of the restriction of trophoblasts to cell-free HIV-1 infection. HIV-1 infection was determined using HXB2 and BaL HIV-1 pseudotyped viruses containing a luciferase reporter gene to measure infection rates. Pseudotyped HIV-1 DEnv and HIV-1 VSV-G viruses were used as negative and positive controls respectively. Proteasomal degradation was inhibited by three different proteasome inhibitors.

Results: Viral internalisation was confirmed by p24 detection in whole cell extracts (WCE) of BeWo cells. The presence of p24 in WCE of cells exposed to envelope-deficient virus suggests that viral internalisation occurs through an endocytic pathway, as opposed to membrane fusion. BeWo cells were exposed in the presence of proteasome-inhibitors to pseudotyped HIV-1 to determine the effect of proteasome inhibition on HIV-1 infection in trophoblast cells. Levels of infection by VSV-G envelope pseudotyped HIV-1 were significantly higher in cells previously exposed to proteasome inhibitors. Conversely, no effect on infection was observed when proteasome-inhibited BeWo cells were exposed to HXB2 or BaL pseudotyped HIV-1.

Conclusions: Our results confirm recent studies indicating that viral entry in trophoblasts occurs via an endocytic pathway, independently of the viral envelope. Additionally, the results suggest that the restriction in trophoblast cells is not exclusively due to proteasomal degradation of incoming virions.