

Interferon- α produced by pDC in the human thymus decreases replication of HIV-1.

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Plasmacytoid dendritic cells (pDC) have been described as the principle producers of interferon- γ (IFN- γ). It is estimated that this population can secrete 200 to 1000 times more IFN- γ than any other white blood cell. Signaling through toll-like receptor 9 (TLR-9), the receptor for unmethylated CpG dinucleotide sequences, is one trigger for IFN- γ release by pDC. pDC have also been shown to secrete IFN- γ in response to viral infection. In addition to its antiviral effect, IFN- γ acts as an autocrine survival factor for pDC. As pDC with the potential to secrete IFN- α are present in the thymus, we evaluated the ability of pDC in the thymus to produce IFN- α in the HIV-1 infected thymus.

Using flow cytometry, we identified pDC in the thymus by their expression of CD45RA, CD4, BDCA2, high levels of the interleukin-3 receptor alpha (CD123), and a lack of CD3 expression. pDC were enriched using AutoMACS and further purified using cell sorting. We found that thymic cell suspensions from postnatal thymus enriched for CD123⁺ cells are capable of secreting high levels of IFN- γ in response to CpG stimulation (CpG 2216), while the CD123-depleted population was unresponsive to CpG. As pDC express TLR9, they are the cells most likely to produce IFN- γ in response to CpG.

We then examined the effect of CpG induced IFN- γ on HIV-1 infection of thymocytes and found that productive HIV-1 infection was decreased in thymic organ cultures treated with CpG and subsequently infected with HIV-1. Similar results were obtained by adding exogenous IFN- α to the cultures. Our data also showed that HIV-1 infection triggered a low level of IFN- γ production. However, the levels of IFN- α were apparently below the level needed for a suppressive antiviral effect, as productive HIV-1 infection (measured by p24 levels in the supernatants) took place. One possible explanation for the inability of pDC to control viral infection is infection of the pDC themselves which may result in the loss of pDC or a decrease in their function. Indeed in the SCID-hu mouse model we found that pDC can be productively infected by HIV-1.

To further elucidate the role of pDC in HIV-1 infection, pDC were depleted from thymocytes and total thymocytes or CD123-depleted cells were infected with HIV-1 and cultured in the presence of IL-7. Depletion of pDC from the thymocytes accelerated HIV-1 replication and led to a more profound loss of CD4⁺ cells.

Our data indicate that thymic pDC can impact HIV replication through the secretion of IFN- α . However, our data also show that natural HIV-1 infection does not induce sufficient quantities of IFN- α to abort viral replication.