Restriction of HIV-1 infection in dendritic cells avoids induction of IFN-α-mediated responses and reduces chemokine expression. Impact on viral escape and establishment of CD4 reservoirs

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Background:
Both immature (IDC) and mature (MDC) dendritic cells display strong restriction to productive HIV1 infection state but are capable of presenting the virus to T cells thereby enhancing the infection of lymphocytes and the spread of virus in the body. The restriction to infection can be overcome by the presence of Vpx protein of HIV2. In this work we analyze the regulation of gene expression in DC infected by HIV-1 in conditions of restrictive (-Vpx) or productive (+Vpx) replication and differences in gene expression between productively infected IDC and MDC.

Methods:
IDC were generated from blood monocytes treated with GM-CSF and IL4. Final differentiation induced with LPS. DCs were infected with NL4.3-Δenv-GFP viral particles VSV-pseudotyped. Vpx was incorporated into virions by co-transfection of a Vpx-expressing plasmid in producer cells. RNA was isolated, labeled and hybridized to a Whole Human Genome Microarray (Agilent). Expression ratios (log2) of mRNA from IDC and MDC were calculated using non-infected cells values as baseline. Only probes with q-value < 5% and 2 fold change were considered as statistically significant.

Results:
The frequency of productive infection increased from 30 to 75% in IDC and from 5 to 20% in MDC with Vpx-virions. Gene expression showed that HIV-1 infection induced interferon (IFN)-responsive gene expression in IDC and down-regulated chemokine genes in MDC.

Major gene expression changes in productively infected by HIV-1			
IDC: Up-regulated molecules	**Fold**	**MDC: Down-regulated molecules**	**Fold**
IFI27	3.85	CXCL10	-4.56
IFI44L	3.6	APOBEC3A	-3.16
IFI6	3.02	CXCL11	-2.94
TCHH	2.59	CXCL9	-2.82
IFIT1	2.46	MYH7	-2.61

[Gene Expression Changes]

Conclusion:
Productive HIV-1 replication in IDC triggers antiviral responses through the induction of IFN-related-genes. Down-regulation of chemokines in MDC cells could potentially prevent transmission of HIV to lymphocytes. Thus, paradoxically, restriction of HIV-1 replication in DC would results in viral escape from IFN-a response and increased transmission to CD4 lymphocytes in the immune synapse, thus increasing the size of CD4 reservoirs.