

Type I Interferons (viral inhibition, immunomodulatory functions)

PE6

Comparison of gene expression profile between human and macaque dendritic cells infected with virus carrying or not Vpx-loaded particles and assessment of their pathogenic impact

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Background: Dendritic cells (DC) are antigen presenting cells that play a central role in the regulation of the immune response and whose functions depend on their stage of differentiation. Besides, DCs are characterized by a highly restrictive environment to HIV-1 replication. Susceptibility of DC to infection by different lentivirus is related with the presence of the Vpx protein that overcomes restriction due to SAMHDI. Current findings suggest that productive infection of immature-DC (IDC) is detected by sensor proteins that activate Interferon-mediated responses that interfere with viral propagation and decrease virulence. However, few data have been provided about mature DC (MDC) infection.

Methods: To get a better insight into the pathogenic consequences of DCs infection we analyzed changes in gene expression with a whole genome microarray when IDC or MDC were productively infected using Vpx-loaded HIV-1 particles. Based on microarray data we performed additional studies using qPCR to analyze transcriptomic changes provoked by infection of human and macaque IDC and MDC in restrictive (HIV-1) and productive (HIV-1+Vpx, HIV-2 and SIVmac) conditions

Results: Strong differences in gene expression were found according to DC differentiation and type of infection. Whereas in IDC productive HIV infection strongly induced class-I-interferon-stimulated-genes such induction was not produced in MDC. In contrast a sharp decrease in CXCR3-binding chemokines was observed when MDC were infected with Vpx-loaded particles and this reduction resulted in decreased trans-infection of CD4 lymphocytes and decline of viral reservoirs. Similar patterns of gene expression were found when dendritic cells were infected with HIV-2 and SIV that naturally express Vpx from their genomes.

Overall these results suggest that, paradoxically, restriction of HIV-1 infection in DCs results in increased virulence through different mechanisms. In IDC, restrictive infection avoids sensing and induction of interferon-mediated responses whereas in MDC the production of CXCR3 binding chemokines is not modified in the absence of productive infection leading to lymphocyte attraction to the immune synapse, enhancement of HIV-1 trans-infection and an increase in viral reservoirs size.

Conclusions: Our data confirm previous observations and propose new pathogenic mechanisms to understand how restriction of HIV-1 replication in DC favors viral dissemination and increased virulence in infected host.