

The intestinal microenvironment affects the susceptibility of DCs to HIV-1

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Background: The intestinal mucosa is the major site of HIV-1 entry and persistence. We previously showed that intestinal colonic dendritic cells (DC) are actively recruited to extend cellular projections across an intact epithelial barrier in response to CCR5-using virus. DCs, being thus a first target for HIV-1 during transmission, may also act as reservoir. However the susceptibility of intestinal DC to HIV infection in the intestinal microenvironment has been poorly investigated, due to difficulties in isolating mucosal DC.

Methods: Myeloid DC (mDC) obtained from the intestinal colonic lamina propria and from blood were identified as Lin (CD3, CD14, CD16, CD56, Cd19)-HLADR⁺ CD11c⁺ cells and further characterized for the expression of HIV-1 receptors. Supernatant obtained from an ex vivo culture of healthy human colonic mucosa was used to condition monocyte-derived DC in an in vitro model as to mimic the exposure of DC to intestinal microenvironment. Conditioned-DC (C-DC) were analyzed by flow cytometry for the expression of HIV-1 receptors and activation markers, and incubated in vitro with either R5 or X4 HIV-1 to study their susceptibility to infection.

Results: C-DC displayed a significant down-regulation of CCR5 and CD4, an up-regulation of CXCR4 and a moderate modulation of DC-SIGN expression compared to unconditioned DC. Intestinal conditioning did not induce activation of the cells. Interestingly, both R5 and X4 HIV-1 replicated less efficiently in C-DC compared to unconditioned DC. Among several cytokines and chemokines analyzed, colonic supernatants contained the CCR5-binding chemokines Mip1b and MCP-1, whereas the CXCR4 ligand SDF-1a was absent. IL-10 and IL-2, described to induce CXCR4 up-regulation on DC, were also detected. Thus, this specific intestinal milieu may determine the observed phenotype. Of note, colonic mDC showed lower CCR5 and higher CXCR4 expression compared to blood derived mDC, and a similar activation profile, which confirmed the results obtained after intestinal conditioning.

Conclusion: The intestinal microenvironment can condition the phenotype of DCs by modulating the expression of the HIV receptors and in turn also the susceptibility to and replication of the virus. Our model is relevant to study the role of mucosal DC in HIV-1 infection, spreading and persistence in the intestinal mucosa.