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Dendritic cell-lymphocyte crosstalk stimulates HIV-1 replication and impairs host restriction factor SAMHD1 in dendritic cells

B. Su[1], M.E. Biedma[1], T. Decoville[1], A. Lederle[1], M. Peressin[1], M. Lambotin[1], A. Proust[1], S. Schmidt[1], G. Laumond[1], V. Holl[1,2], C. Moog[1]

[1]*INSERM U1110, Institut de Virologie, Faculté de Médecine, Université de Strasbourg, Strasbourg, France,*

[2]*Covance CLS SA, Lab Science Department, Hematology and Flow Department, Geneva, Switzerland*

Background: HIV-1 restriction factor SAMHD1 is counteracted by the viral protein Vpx of HIV-2 or SIV_{sm} /SIV_{mac} but no such viral protein was identified in HIV-1, leading to high restriction of HIV-1 replication in dendritic cells (DCs). Interestingly, we observed a stimulation of HIV-1 replication when DCs were cocultured with primary CD4 T or B lymphocytes suggesting that the HIV-1 restriction in DCs was reduced during DC/lymphocyte crosstalk. The aim of this study was to understand SAMHD1-mediated restriction in DC/lymphocyte coculture.

Methods: Primary monocyte-derived DCs were infected with various R5 HIV-1 primary isolates during 2h, and then cocultured with autologous activated or non-activated CD4 T and B lymphocytes. We distinguished the DCs from lymphocytes by specific membrane staining. After 48h and 72h, the percentages of infected DC-$SIGN^+$ $CD3^-$ MoDCs, $CD3^+$ DC- $SIGN^-$ CD4 T and $CD20^+$ DC-$SIGN^-$ B lymphocytes were determined based on detection of intracellular viral p24 antigen by flow cytometry. Simultaneously, the expression of intracellular SAMHD1 was quantified in DCs. Virus-like particles containing Vpx (VLP-Vpx) and exogenous dNTPs were used as control to decrease SAMHD1 expression and to stimulate HIV-1 replication, respectively.

Results: We found that SAMHD1 expression in DCs was significantly decreased from 80% to 10% when DCs were cocultured with CD4 T or B lymphocytes for 48h and 72h ($p< 0.01$ and $p< 0.05$ respectively, $n\geq 6$). Moreover, this decreased expression of SAMHD1 was correlated with an increase HIV-1 replication in cocultured DCs. As controls, VLP-Vpx increased HIV-1 replication and decreased SAMHD1 expression, and addition of exogenous dNTPs to the culture increased HIV-1 replication but without modifying SAMHD1 expression in DCs.

Conclusion: These results demonstrate that CD4 T and B lymphocytes decrease the expression of SAMHD1 in DCs leading to significant HIV-1 replication in these cells. It suggests that HIV-1 restriction factor SAMHD1 could be counteracted by DC/lymphocyte crosstalk and inhibition of this crosstalk would prevent DCs from HIV-1 infection. Therefore, HIV-1 replication and restriction in DCs should be considered in more physiologically relevant models of DC/lymphocyte coculture. This work was supported by EuroNeut41 (FP7-HELTH-2007-A-201038) grant, Dr O. Schwartz kindly provided Ab against human SAMHD1 and VLP-Vpx.