Le document est disponible en accès libre à l'adresse URL suivante :
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4635491/

Journal of General Virology (2015), 96, 1463–1477 DOI 10.1099/vir.0.000065

Nef promotes evasion of human immunodeficiency virus type 1-infected cells from the CTLA-4-mediated inhibition of T-cell activation

Mohamed El-Far,[1,2] Petronela Ancuta,[1,2] Jean-Pierre Routy,[3] Yuwei Zhang,[1,2,4] Wendy Bakeman,[4] Rebeka Bordi,[1,4] Sandrina DaFonseca,[1,2,4] Elias A. Said,[1,2]† Annie Gosselin,[1] Tévy-Suzy Tep,[1,2] Quentin Eichbaum,[5] Julien van Grevenynghe,[1,2,4] Olivier Schwartz,[6] Gordon J. Freeman,[7] Elias K. Haddad,[1,4] Nicolas Chomont[1,2,4] and Rafick-Pierre Sékaly[1,2,4,8]

Correspondence
Nicolas Chomont
nchomont@vgtiflorg
Rafick-Pierre Sékaly
rafick.sekaly@gmail.com

[1]Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada

[2]Department of Microbiology, Infectiology and Immunology, Université de Montréal, Québec, Canada

[3]Division of Hematology and Chronic Viral Illness Service, McGill University Health Centre, McGill University, Montréal, Québec, Canada

[4]Vaccine & Gene Therapy Institute Florida, Port St Lucie, FL, USA

[5]Vanderbilt University, School of Medicine, Nashville, TN, USA

[6]Virus and Immunity Group, Department of Virology, Institut Pasteur, Paris, France

[7]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

[8]Case Western Reserve University, Cleveland, OH, USA

CTLA-4 is a negative regulator of T-cell receptor-mediated $CD4^+$ T-cell activation and function. Upregulation of CTLA-4 during human immunodeficiency virus type 1 (HIV-1) infection on activated T cells, particularly on HIV-specific $CD4^+$ T cells, correlates with immune dysfunction and disease progression. As HIV-1 infects and replicates in activated $CD4^+$ T cells, we investigated mechanisms by which HIV-1 modulates CTLA-4 expression to establish productive viral infection in these cells. Here, we demonstrate that HIV-1 infection in activated $CD4^+$ T cells was followed by Nef-mediated downregulation of CTLA-4. This was associated with a decreased T-cell activation threshold and significant resistance to CTLA-4 triggering. In line with these *in vitro* results, quantification of pro-viral HIV DNA from treatment-naive HIV-infected subjects demonstrated a preferential infection of memory $CD4^+CTLA\text{-}4^+$ T cells, thus identifying CTLA-4 as a biomarker for HIV-infected cells *in vivo*. As transcriptionally active HIV-1 and Nef expression *in vivo* were previously shown to take place mainly in the $CD3^+CD4^-CD8^-$ [double-negative (DN)] cells, we further quantified HIV DNA in the $CTLA\text{-}4^+$ and $CTLA\text{-}4^-$ subpopulations of these cells. Our results showed that DN T cells lacking CTLA-4 expression were enriched in HIV DNA compared with DN $CTLA\text{-}4^+$ cells. Together, these results suggested that HIV-1 preferential infection of $CD4^+CTLA\text{-}4^+$ T cells *in vivo* was followed by Nef-mediated concomitant downregulation of both CD4 and CTLA-4 upon transition to productive infection. This also highlights the propensity of HIV-1 to evade restriction of the key negative immune regulator CTLA-4 on cell activation and viral replication, and therefore contributes to the overall HIV-1 pathogenesis.

Received 3 October 2014
Accepted 19 January 2015