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► **To cite this version:**

O Manches, D Munn, A Fallahi, J Lifson, Laurence Chaperot, et al.. P16-52. HIV-activated human plasmacytoid DCs induce Tregs through an indoleamine 2,3-dioxygenase-dependent mechanism. *Retrovirology*, 2009, 6 (Suppl 3), pp.P281. inserm-00651123

HAL Id: inserm-00651123

<https://inserm.hal.science/inserm-00651123>

Submitted on 12 Dec 2011

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Poster presentation

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PI6-52. HIV-activated human plasmacytoid DCs induce Tregs through an indoleamine 2,3-dioxygenase-dependent mechanism

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from AIDS Vaccine 2009
Paris, France. 19–22 October 2009

Published: 22 October 2009

Retrovirology 2009, 6(Suppl 3):P281 doi:10.1186/1742-4690-6-S3-P281

This abstract is available from: <http://www.retrovirology.com/content/6/S3/P281>

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Background

Plasmacytoid dendritic cells (pDC) are crucial cells implicated in anti-viral immune responses. On recognizing HIV, they become activated, secreting high amounts of IFN α and inflammatory cytokines, thereby potentiating anti-viral innate and adaptive immune responses. However, the role of pDC in adaptive immunity is still debated. Several studies have documented a role for activated pDC in the induction of CD4⁺ or CD8⁺ regulatory T cells (Treg), both in vitro and in vivo. A direct correlation between CD8⁺ T cell activation levels and disease progression levels has been confirmed in many studies. We investigated here whether HIV-stimulated pDC can regulate the levels of immune activation by promoting the differentiation of regulatory CD4⁺ T cells.

Methods

Freshly purified pDC from normal donors (New York Blood Bank) were incubated for 7 days with purified allogeneic CD4⁺ CD25⁻ T cells, and their suppressive activity measured in a secondary proliferative assay. CD86/CD83 expression and cytokine secretion by monocyte-derived DC (moDC) induced by LPS or R848 were measured in presence or absence of CD3-activated Treg. siRNA knock-down of NIK and IKK α was performed on the leukemic pDC line GEN2.2 and expression of IDO was monitored at the RNA and protein level.

Results

HIV-stimulated pDC were found to induce the differentiation of Treg from naive CD4⁺ T cells, in an indoleamine 2,3 dioxygenase (IDO)-dependent way. Furthermore, pDC-induced Treg could suppress the Toll-Like Receptor (TLR)-mediated maturation of moDC, partially through CTLA-4 interaction with CD80/CD86. We further show that TLR triggering induces the activation of IDO through the non-canonical NF- κ B pathway, as evidenced by knocking-down the expression of NIK and IKK α .

Conclusion

This study reveals what we believe to be a novel mechanism by which pDC may regulate and potentially limit anti-HIV immune responses, and identifies a potential target for clinical intervention.