REVERSION OF CD4+ T-CELL EXHAUSTION MEDIATED BY PLASMACYTOID DENDRITIC CELLS AFTER TOLL LIKE RECEPTORS AGONIST STIMULATION

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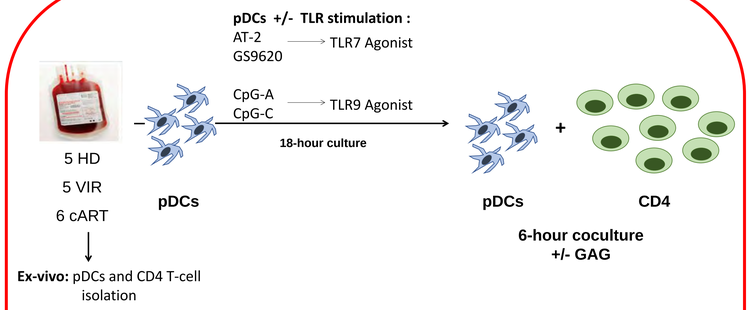
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INTRODUCTION

T-cell exhaustion is not reverse by effective combination antiretroviral treatment (cART). T-cell exhausted cells have been associated with HIV persistence during cART. The plasmacytoid dendritic cells (pDCs) sense viral and bacterial products through Toll-like receptors (TLR)-7 and -9 and translate this sensing in IFN-α production and T-cell polarization. It is unknown whether pDCs can reverse T-cell exhaustion in HIV-infected patients on long-term suppressive ART.

The aim of the present study was to analyze, through a pDC/T-cell co-culture, whether pDCs after stimulation with different TLR agonists were able to reverse T-cell exhaustion.

MATERIALS AND METHODS

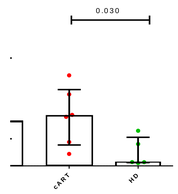


Patients on suppressive cART (cART, n=6) were compared with healthy donors (HD, n=5) and viremic patients naive for cART (VIR, n=5). pDCs and CD4+ T-cells were isolated from 450mL of whole blood using magnetic negative selection. After pDC overnight stimulation with HIV inactivated with aldrithiol (AT-2-HIV), CpGA, CpGC, and GS9620 or no stimuli (NS), pDCs were cocultured for 6h with autologous CD4+ T-cells.

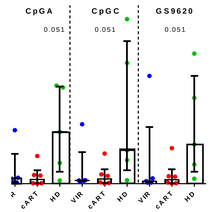
The expression of PD-1, TIGIT, TIM-3 and LAG-3 in different T-cell subsets was quantified *ex vivo* and *in vitro* and intracellular cytokine staining of IL2, INFγ, TNFα and IL17a was performed to assess polyfunctionality by multiparametric flow cytometry.

RESULTS

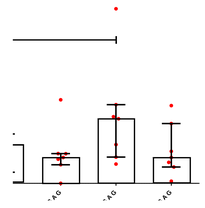
1_ *Ex vivo* the expression of PD1, TIGIT, TIM3 or LAG3 were increased in several CD4+ T-cell memory subsets from cART compared to HD.



2_ After coculture with autologous CD4+ and stimulated pDCs with TLR-7 and-9 agonist we observed differences in the expression of exhaustion markers. While, PD1 and TIM3 in patients on suppressive cART normalized their expression respect to healthy donors. LAG3 and TIGIT decreased their expression respect healthy donors.



3_ After the GAG stimulation, we observed differences in the expression of the single cytokines production. Increased levels of IL2, IL17a, INFγ and TNFα were observed after stimulation of TLR-7 and -9 ligands respect non-stimulated condition in patients on suppressive cART.



4_ Polyfunctionality index (Pindex) of CD107a, IL2, INFγ, TNFα and IL17a under GAG stimulation was calculated. An increase in the polyfunctionality of different CD4+ T-cell subsets in terms of multiple cytokines production were observed. Patients on suppressive cART showed increased levels of polyfunctionality after stimulation with agonist of TLR-7 and -9 respect non-stimulated condition.

DISCUSSION

The modulation of the pDCs through TLR agonists allow partial reversal CD4+ T-cell exhaustion in HIV-infected patients on ART. These results may have important implications in the reduction of deleterious effect of pDCs and T-cells causing non AIDS events and may decrease HIV-reservoir levels.

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