Altered PD-1/PD-L1 Interactions in Germinal Centers of treated HIV infected subjects

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Abstract

Background. The establishment of an HIV latent reservoir is the major obstacle to achieve HIV eradication and cure. In fact the latent reservoir cannot be targeted by the host immune response and/or by ART. We have recently demonstrated active HIV transcription in lymph node (LN) PD-1$^+$/T follicular helper T (Tfh) cells in aviremic long-term ART treated individuals. The levels of HIV transcription in PD-1$^+$/Tfh cells was significantly higher as compared to any other blood and LN memory CD4 T-cell populations. On the basis of this observation, we have hypothesized that increased HIV transcription in Tfh cells may rely on the reduction in the inhibitory signal delivered through PD-1/PD-L1 interaction in the germinal centers (GCs).

Methods. In order to test this hypothesis, we assessed 1) the expression of PD-1 and PD-L1 in blood and LN cell populations by mass cytometry and immunohistochemistry (IHC) and 2) the impact of PD-1/PD-L1 interaction on HIV production in blood and LN memory CD4 T cells of viremic and ART-treated aviremic HIV-infected subjects.

Results. We show that PD-1 was largely expressed in blood and LN memory CD4 T-cell populations and particularly in Tfh cells. In contrast, PD-L1 expression was predominant in extra-follicular areas and restricted to macrophages and dendritic cells (P<0.05). Interestingly, IHC revealed that PD-1/PD-L1 ratio was significantly higher in GCs as compared to extra-follicular areas of treated aviremic HIV-1 infected subjects (P<0.05). In addition, PD-1/PD-L1 ratio in GCs was about 20 fold higher in treated than viremic HIV-1 infected subjects (P<0.05) thus suggesting that PD-1/PD-L1 interactions might be altered in GCs of treated HIV-infected subjects. We then showed that TCR-mediated HIV production from latently infected memory CD4 T cells was significantly inhibited in presence of PD-L1 recombinant protein (P<0.05) thus indicating that PD-1/PD-L interactions substantially reduced TCR-induced HIV production. Finally, we demonstrated that anti-PD-1 mAbs pembrolizumab efficiently reactivated HIV replication from latently infected blood memory CD4 T cells (P<0.05).

Conclusions. This study suggests that an imbalance in the PD-1/PDL-1 signaling may contribute to the persistence of HIV in memory CD4 T cells and to the presence of active HIV transcription in LN Tfh cells. Taken together, these data provide the rationale for the development of intervention strategies targeting PD-1 and/or PDL-1 to reactivate HIV replication.

Results

Figure 1 : IC-molecule expression on blood and LN CD4 T-cell populations by mass cytometry (MC)

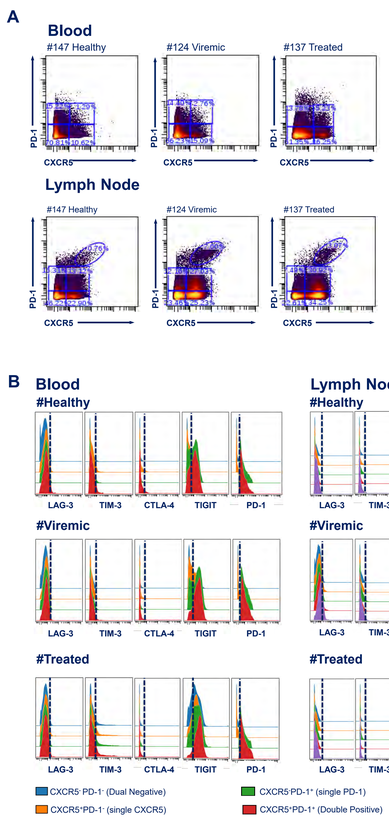


Figure 2 : IC-ligand expression on blood and LN cell populations by MC

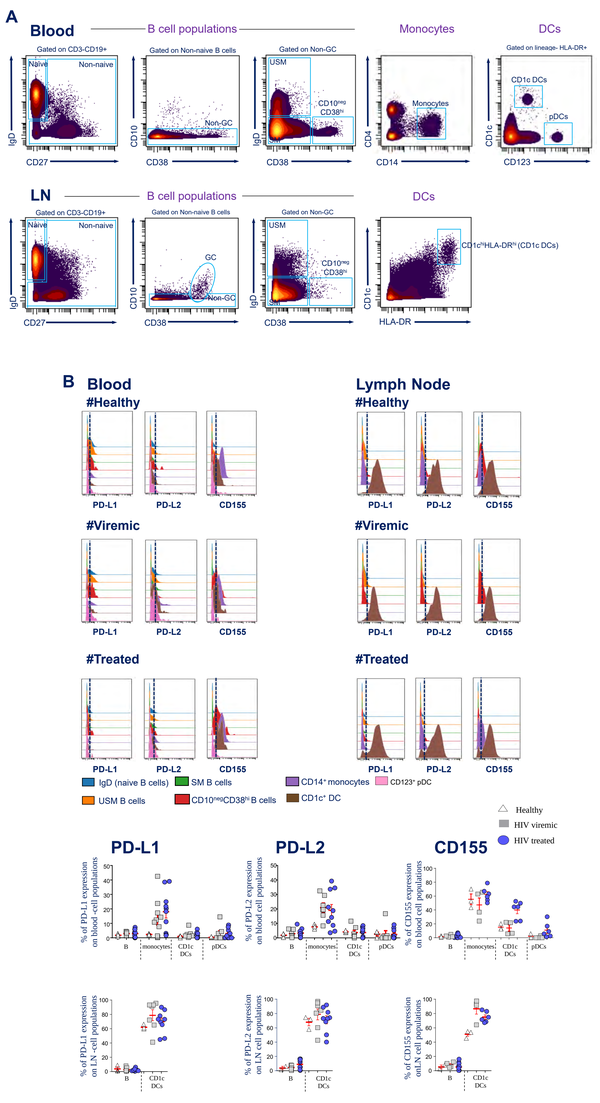


Figure 3: Localization of histopathological changes associated with HIV-1 infection and ART treatment in LN tissues

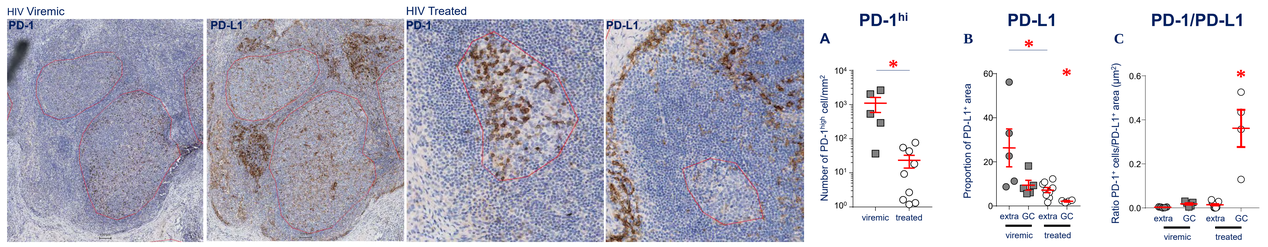


Figure 4 : Impact of recombinant IC-Ligands on CD4 T cell proliferation and HIV production from blood and Lymph node

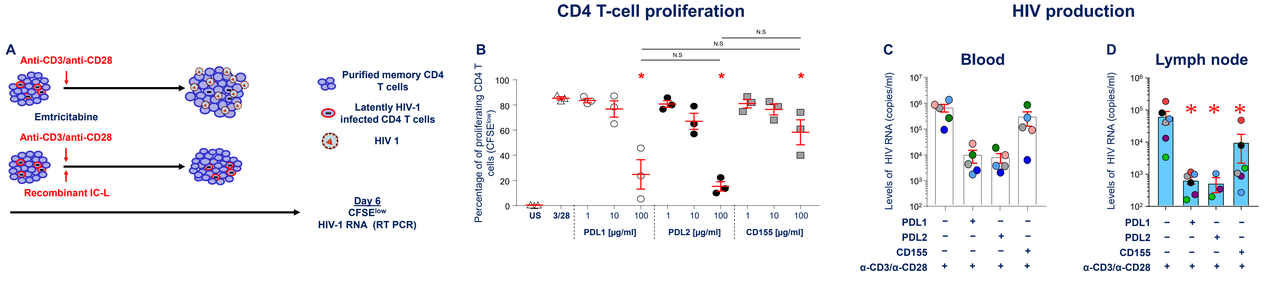
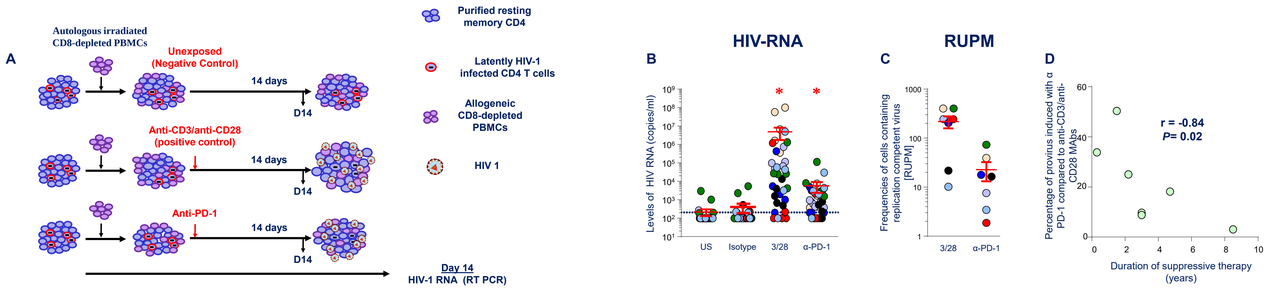


Figure 5: Anti-PD-1 MAb, Pembrolizumab, reactivates HIV replication from latently infected blood memory CD4 T cells *in vitro* and provirus induced with Pembrolizumab treatment correlates with duration of suppressive HAART



In the present study, we demonstrated that

1) TIGIT and PD-1 are the major IC molecules expressed on blood and LN CD4 T-cell populations of treated individuals; 2) IC Ligands for the majorly expressed IC molecules *i.e.* PDL1, PDL2 and CD155 are predominantly expressed on monocytes and DCs from blood and LN of treated individuals; 3) IC molecule-Ligand interaction impacts TCR-mediated HIV transcription and production from memory CD4 T cells of treated individuals; 4) IC-ligand expression within GC areas of LNs of treated individuals is altered 4) IC molecule-Ligand interaction can be blocked to reactive latently infected blood memory CD4 T cells from treated individuals.