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ORAL PRESENTATION

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Purging the HIV-1 reservoir through the disruption of the PD-1 pathway

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Background

The main obstacle to HIV-1 eradication is a small pool of T_{CM} (central memory) and T_{TM} (transitional memory) latently infected CD4⁺ T cells that persist in patients receiving HAART. The mechanisms implicated in the establishment and persistence of the HIV reservoir are still unknown. The PD-1 receptor is expressed by CD4⁺ T cells from HIV-infected patients, and efficiently inhibits T cell proliferation. Here, we investigate a possible role for this receptor in the establishment and maintenance of a cellular reservoir for HIV.

Methods

PBMCs were obtained by leukapheresis from HAART-naïve, chronically HIV-1-infected subjects and were subjected to total CD4⁺ T cells negative selection. Viral production was induced through TCR triggering (CD3/CD28) with or without co-triggering of the PD-1 pathway with an Ig-PD-L1 chimera. Cell culture supernatants were serially harvested; viral release was quantified by QRT-PCR or p24 ELISA. The frequency of CD4⁺ T cells harbouring HIV DNA was determined by Q-PCR.

Results

Cell sorting and Q-PCR experiments showed that PD-1^{high} cells from viremic donors preferentially harbour HIV-1 integrated DNA when compared with their PD-1^{low} counterparts, indicating that these cells constitute a preferential reservoir for the virus. Triggering of the PD-1 pathway inhibits 50% of HIV-1 production in primary CD4⁺ T cells at day 1 and up to 95% at day 3. Importantly, this inhibition was restricted to PD-1^{high} cells, demonstrating the specificity of this mechanism. Moreover, we observed

that the disruption of the PD-1/PD-L1 interaction enhances the spontaneous release of HIV-1 virions by CD4⁺ T cells.

Conclusions

Our results suggest that: (1) the PD-1 receptor can be used as a specific marker to target the HIV-1 reservoir; (2) viral production is inhibited after triggering of the PD-1 receptor; and (3) viral production was enhanced after blocking of this inhibitory pathway. Altogether, our results demonstrate a crucial role for PD-1 in the establishment.

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