PD-1 identifies latently HIV-infected non-proliferating and proliferating CD4⁺ T-cells

Van der Sluis RM, Kumar NA, Evans VA, Sékaly RP, Fromentin R, Chomont N, Cameron PU and Lewin SR

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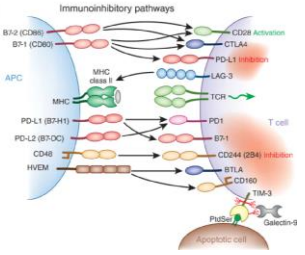
THE UNIVERSITY OF MELBOURNE

Doherty Institute

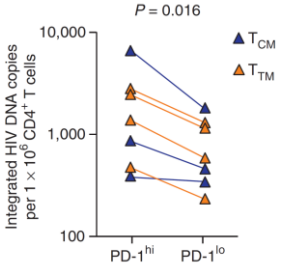
Introduction

- Immune checkpoint (IC) markers dampen the immune response
- IC are expressed on T-, B- and NK cells and IC ligands on antigen presenting cells (APC)
- Different mechanisms of inhibition:
  - ligand competition
  - ligand internalization
  - negative signaling



Freeman & Sharpe, Nature Immunology 2012

Introduction



- CD4⁺ T-cells from HIV-infected individuals on ART expressing the IC PD-1, are preferentially infected

Chomont et al., Nature Med 2010

Hypothesis and aims

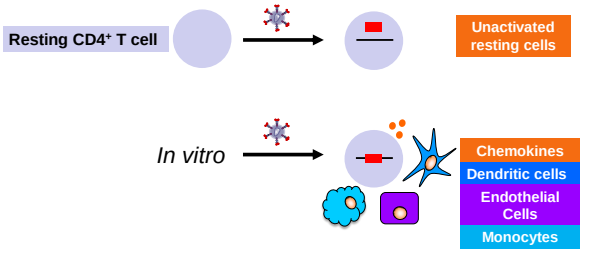
Expression of IC during APC-T cell interactions may actively suppress viral replication and maintain latency

Aim 1: Determine the expression of different IC on CD4⁺ T cells, and their ligands on DC and monocytes, in our *in vitro* APC-T cell model for latency

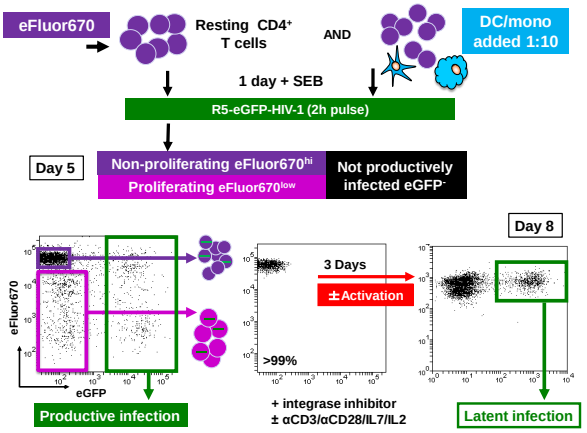
Aim 2: Identify whether there is latency enrichment in non-proliferating and proliferating CD4⁺ T cells expressing IC following APC-T cell interaction

Aim 3: Determine the effects of blocking IC/IC ligands on the establishment/maintenance of latency in resting CD4⁺ T cells

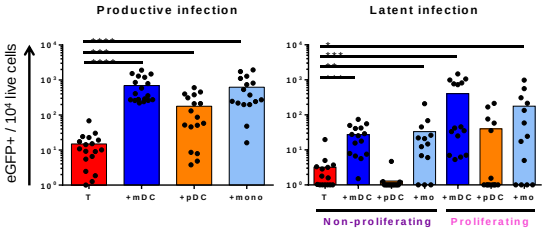
Infection of resting CD4⁺ T cells



Swiggard et al., *J Virol* 2005; Lassen et al., *Plos One* 2012;
Saleh et al., *Blood* 2007; Cameron et al., *Proc Natl Acad Sci* 2010;
Shen et al, J. Virology, 2013; Evans et al, Plos Path, 2013, Ho *et al.*, Cell 2013,
Kumar *et al* Retrovirology [in press]

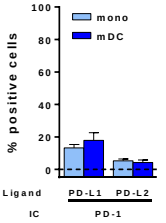


Induction of latency in proliferating and non-proliferating T-cells by mDC and monocytes

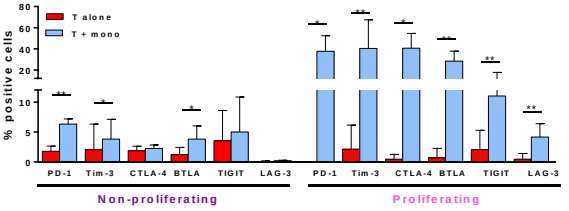


Kumar *et al* Retrovirology [in press]

IC ligands are expressed by mDC and monocytes

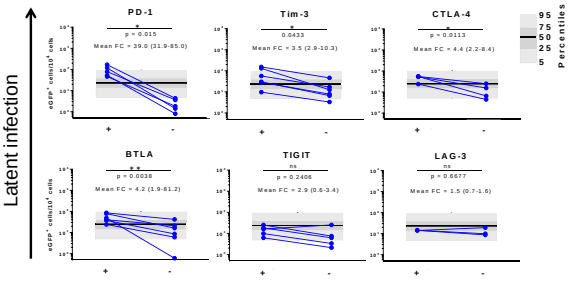


IC expression on proliferating and non-proliferating T cells is enhanced following monocyte co-culture



Latent infection is enriched in proliferating and non-proliferating cells that express PD-1

Sorted eGFP⁻ **non-proliferating** CD4⁺ T-cells following co-culture with monocytes



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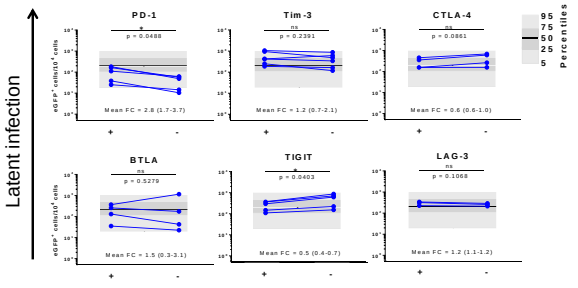


Conclusions

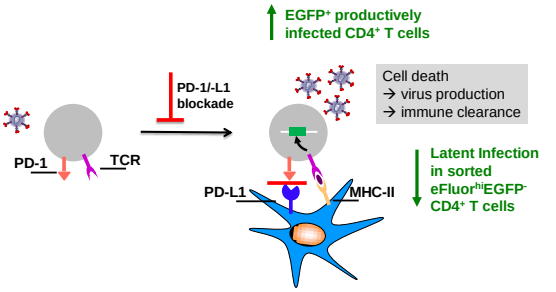
- Myeloid DC and monocytes showed comparable IC ligand expression levels
- IC markers are differently expressed on proliferating and non-proliferating T cells following co-culture with monocytes
- HIV latency is enriched in **non-proliferating** cells expressing high levels of **PD-1**, **Tim-3**, **CTLA-4** or **BTLA** but not LAG-3 or TIGIT
- HIV latency is enriched in **proliferating** CD4⁺ T cells expressing high levels of **PD-1**

Renee.van@unimelb.edu.au

Implications

- APC may facilitate ongoing latent infection of resting CD4⁺ T cells leading to replenishment of the reservoir
- Characterizing the role of PD-1 and other IC in HIV persistence during ART may identify potential targets for eliminating latently infected T cells

Blocking interactions between IC and their ligands *in vitro*



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