Anti-PD-1 disrupts HIV latency in non-proliferating but not in proliferating T-cells

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Conflicts of interest

• Investigator initiated industry funded studies from
  – Viiv Healthcare
  – Gilead Sciences
  – Merck
  – Tetralogic

• Participation in educational activities or consultancies (paid to my institution) from
  – Viiv Healthcare
  – Gilead Sciences
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  – Calimmune
Background

- In HIV-infected individuals on ART, HIV is enriched in PD-1hi cells and cells that express multiple immune checkpoint markers \(^1,2\)

- Anti-CTLA-4 (ipilimumab) increased cell associated unspliced HIV RNA in vivo, consistent with latency reversal \(^3\)

- The combination of anti-PD-1 and anti-CTLA-4 has enhanced potency in the management of metastatic melanoma \(^4\)

Could combination immune checkpoint blockade be used to reverse latency and enhance HIV-specific T-cell function as a strategy for cure?

In vitro model for HIV latency

- eFluor670 labelled rCD4+ T-cells + mo + mDC
- EGFP+ HIV
- Days post infection

Productive infection:
- eFluor670hi EGFP+
- Days 0-2

Non-proliferating infection:
- eFluor670lo EGFP-
- Days 3-5

Proliferating infection:
- eFluor670lo EGFP-
- Days 6-8

- rCD4+ T-cells = resting CD4+ T-cells; SEB = Staphylococcal Enterotoxin B
- mo = monocytes; mDC = myeloid DC
- IC = immune checkpoint; RAL = raltegravir

Evans et al., Plos Path 2013; Kumar et al., Retrovirology 2016

+ IC blocker
+-/− SEB
+ T20+ RAL
Immune checkpoint markers are expressed at high levels in proliferating T-cells following co-culture with monocytes.
Proliferating T-cells co-express multiple immune checkpoint markers

ICM = PD1+Tim3+TIGIT
Latency reversal in non-proliferating cells is possible in the presence of SEB or with multiple IC blockers.
Proliferating cells: latency reversal is only possible with multiple IC blockers

* p<0.05, ** p<0.01, student t test, ICB compared to isotype ctrl

N = 6, black lines are mean values ± SEM
Anti-PD-1 (nivolumab) reverses HIV latency in vivo

Metastatic melanoma
HIV RNA < 20
CD4= 620 cells/ul
On ART for 8 years

cART

CA-US HIV RNA (copies per million 18s)

-1 +1 +7
Ipilimumab

-1 +1 +7
-1 +1 +7
-1 +1 +7
Summary

- Anti-PD-1 can reverse latency in vivo and in vitro but the effects differed in prolifering and non-prolifering latently infected cells.

- In vitro, latency reversal with anti-PD-1 was only seen with the addition of:
  - T-cell activation (SEB) or
  - Combination immune checkpoint blockade

- Co-expression of IC markers, especially on prolifering latently infected cells, may limit the potency of using anti-PD-1 alone for latency reversal.

- Anti-PD-1 alone and in combination with other ICBs, should be further explored in clinical trials as a strategy to reverse latency.
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Non-proliferating cells: latency reversal is possible with anti-PD1 in the presence of SEB

US = unstimulated;

* p<0.05, ** p<0.01, student t test

N = 6, black lines are mean values ± SEM