Highly Dampened HIV-specific Cytolytic T cell Responses Define Viremic Non-progression

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BACKGROUND

Viremic Non-Progressors (VNPs) are a distinct group of HIV-1 infected individuals who remain asymptomatic for several years (>7 years) and have good preservation of CD4 count without ART treatment but display high viral replication. We recently reported that CD4 central memory preservation along with intact thymic repopulation are key homeostatic mechanism resisting CD4 depletion in VNPs. In this study we attempted to identify gut trafficking potential and virus specific functional attributes that could underlie the paradoxical virus-host equilibrium observed in VNPs.

STUDY GROUPS

	Viremic Controllers [VC, n= 07]	Viremic Non-progressor [VNP, n= 12]	Putative Progressors [PuP,n= 11]
CD4+ T cell count (cells/µl)	900 (501- 1469)	680 (501 - 910)	553 (514-908)
Viral Load (log_{10}copies/ml)	2.95 (1.73-3.04)	4.73 (4.01-5.35)	4.71 (3.58-5.98)
Duration of infection (Years)	10 (8 - 24)	10 (7 - 16)	1 (0.5 – 03)
ART	--	--	--

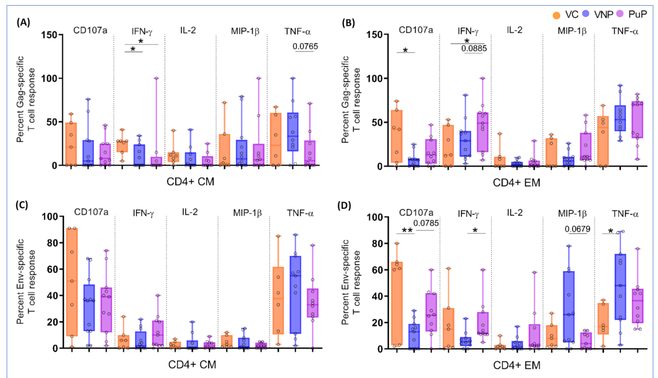
METHODS

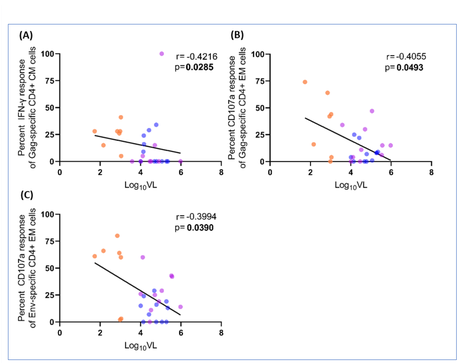
- ***CD107a (cytotoxicity marker), IFN-γ, IL-2, TNF-α (cytokines) and MIP-1β (chemokine)*** were quantified following stimulation of thawed PBMCs with overlapping HIV1 Gag and Env peptides
- HIV-specific responses were obtained for following T cell compartments:
  - ***CD4+ central memory (CM) (CCR7+CD45RA-)***
  - ***CD4+ effector memory (EM) (CCR7-CD45RA-)***
  - ***CD8+ effector memory (EM) (CCR7-CD45RA-)***
  - ***CD8+ terminally differentiated(TD)(CCR7-CD45RA+)***
- Responses shown in result section are background-subtracted using the CD28/49d negative control
- Additionally, ex-vivo immunophenotyping of thawed PBMCs was performed to understand ***CCR5 (HIV Co-receptor)*** and ***integrin α4β7 (Gut trafficking marker)*** level on different CD4 and CD8 T cell subsets.

HIV-specific T cell responses in ***Viremic Non-progressors*** are modulated towards a dominant ***non-cytotoxic response*** enriched for ***MIP-1β production*** with concomitantly dampened degranulation ability.

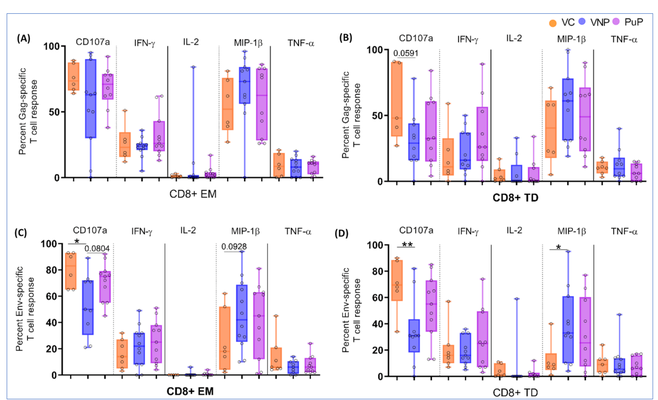
RESULTS

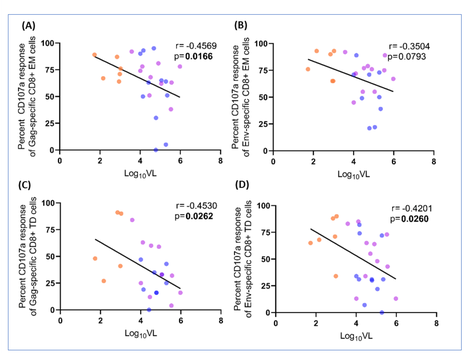
Gag-specific IFN-γ response in CD4+ CM compartment associates with viremic control while dampened Env-specific CD107a response in CD4+ EM characterizes VNPs



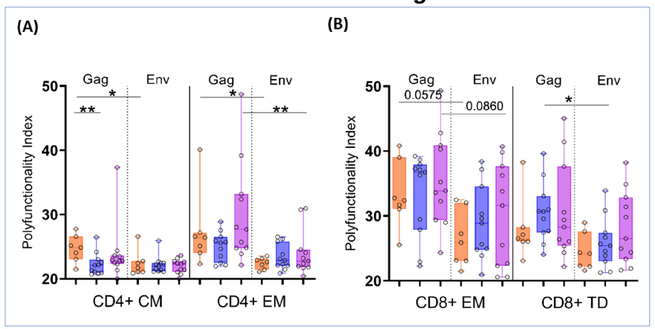


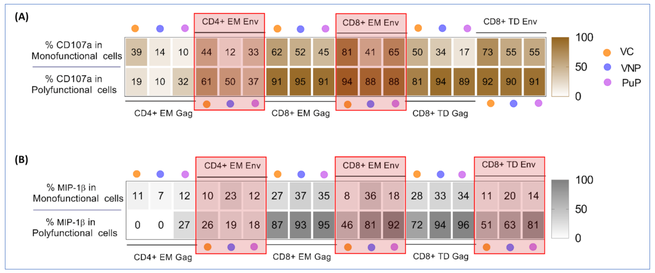
In CD8 compartment, VNPs tend to maintain lower proportion of Env-specific CD107a response while keeping higher proportion of MIP-1β response similar to PuPs



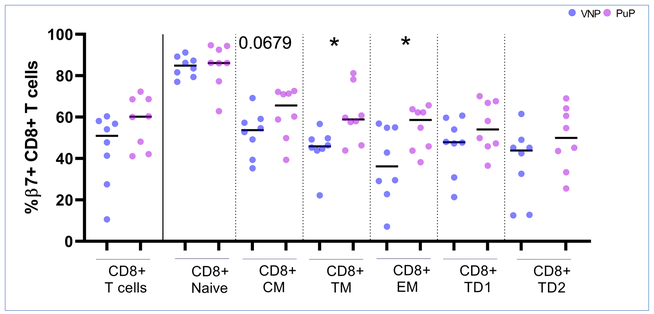


Cytolytic activity is primarily limited to polyfunctional cells in Viremic Non-Progressors





Reduced frequency of β7 expressing (gut homing) CD8 memory subsets suggested a reduced gut pathology in VNPs



CONCLUSION

- Modulation of HIV-specific response in VNPs towards a dominant non-cytolytic response seems to underlie the paradoxical virus-host equilibrium observed in VNPs who remain asymptomatic despite robust viral replication
- Understanding the complex mechanism underlying protection in VNPs may allow immunotherapeutic interventions to achieve functional cures in the context of ART resistance.