Trained immunity features in NK cells of HIV-1 elite controllers

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BACKGROUND

The presence of natural Killer cells (NKs) with memory features have been associated with increased responsiveness upon secondary exposure to viral infectious agents. Memory features within innate immune cells has been attributed to a phenomenon named as trained immunity. Here, our aim is to investigate whether NKs of EC have trained immunity features.

METHODS

Double case-control design

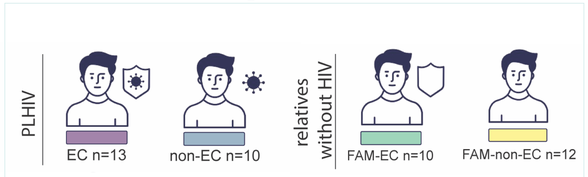


Figure 1. Elite controllers (EC) and normal progressors on ART (non-ECs); 1st degree family members (FAM) of EC and FAM of non-ECs.

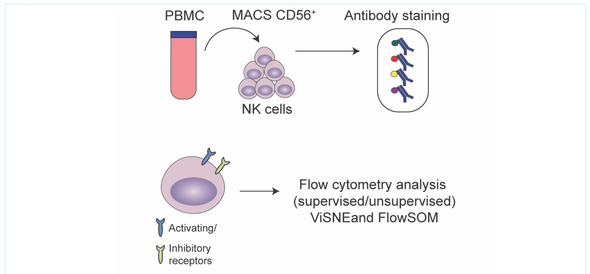


Figure 2. NKs flow cytometry on CD56+ sorted NKs. Live/Dead, HLA-DR, CD3, CD45, CD56, CD16, CD57, CD94, NKG2A, NKG2C, NKG2D, ILT2 (LILRB1), KIR2DL2/3, DNAM, NKp30 and NKp46 markers were assessed.

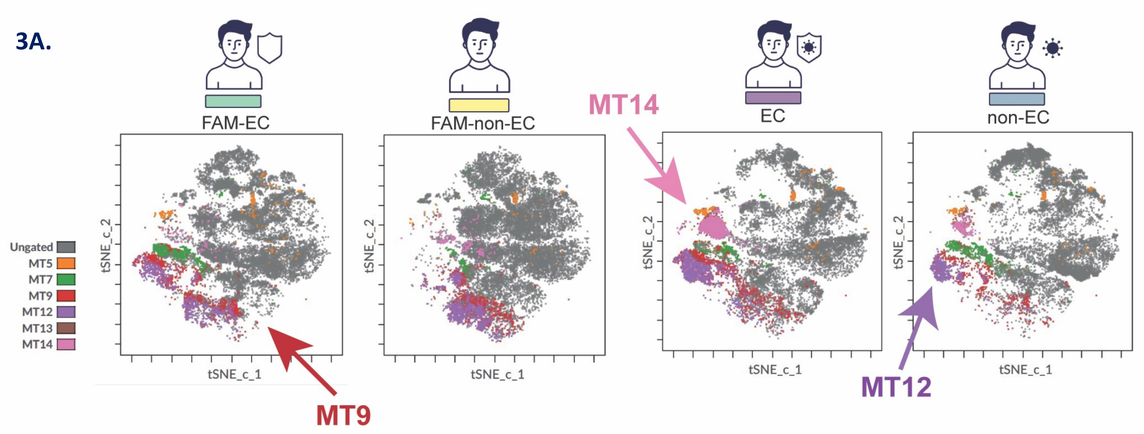
Table 1. Demographics of the participants.

	EC	Non-EC	FAM-EC	FAM-non-EC
Male sex (%)	8 (61.5)	9 (90)	3 (30)	3 (25)
Median age (IQR)	52 (41-67)	55.5 (54-58)	51 (46.8-59.5)	53 (48-71)
Relation (%)				
Sibling	-	-	8 (80)	9 (75)
Parent	-	-	1 (10)	1 (8.3)
Child	-	-	1 (10)	2 (16.7)
CMV IgG (%)	13 (100)	10 (100)	6 (60)	5 (41.7)

The persistence of **memory NK cells** expressing **NKG2C** is associated to spontaneous **HIV control**

RESULTS

Unsupervised analysis (FlowSOM) identifies metaclusters enriched for NKG2C+ NK cells



Distinct profiles of NK cells expressing NKG2C are increased in ECs and 1st degree relatives

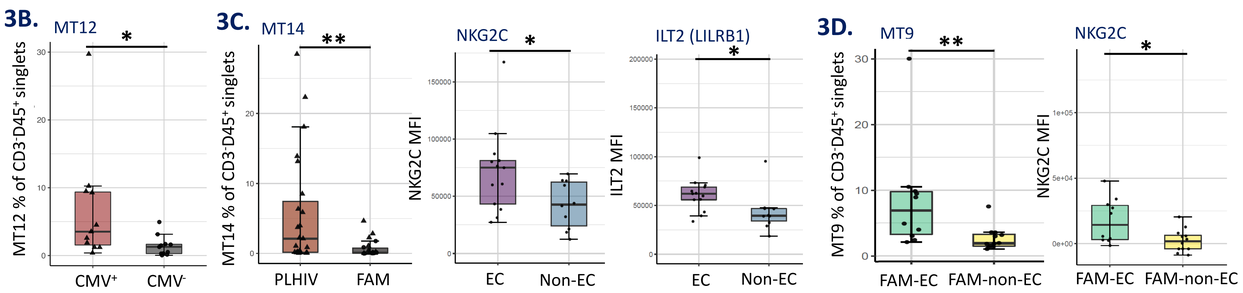


Figure 3. A. NKG2C enriched metaclusters across the study participants. **B.** Percentages of CD57highNKG2ChighKIR2high NK cells were specific to CMV-seropositivity (MT12).
C. Percentages of CD57highNKG2ChighKIR2low NK cells were specific to PLHIV (MT14); NKG2C and ILT2 MFI. **D.** Percentages of NKG2ChighKIR2high NK cells were present in FAM-ECs (MT9); NKG2C MFI.

Increased H3K4me3 at the promoter of *KLRC2* (NKG2C) in EC

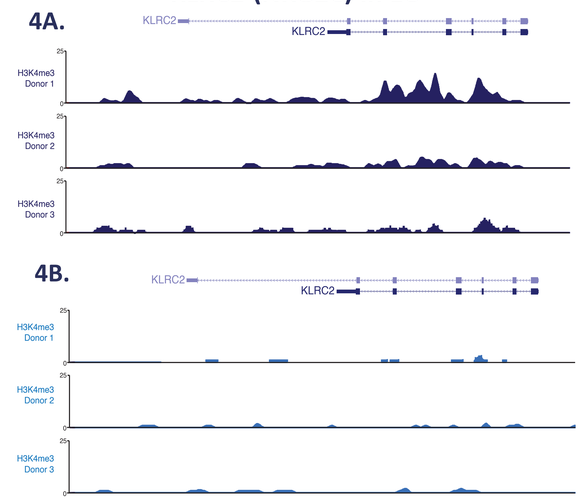


Figure 4. ChIP-seq data of NK cells isolated from **A**. ECs and **B.** non-ECs. Tracks of H3K4me3 peaks near *KLRC2*.

CONCLUSIONS

- A specific NK cells subpopulation expressing NKG2C and ILT2 is associated to HIV control.
- The increased NKG2C expression in 1st degree relatives of ECs indicates the presence of protective responses prior HIV acquisition.
- Epigenetics contributes to the maintenance of NKG2C expression in NK cells of ECs.
- Long-term persistence of NK cells in a memory state - trained NK cells - might favor an optimized secondary response leading to HIV control.

ADDITIONAL KEY INFORMATION

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