THE ROLE OF ADAPTIVE NK CELLS DURING ACUTE HIV-1 INFECTION WITH DIFFERENT SUBTYPES

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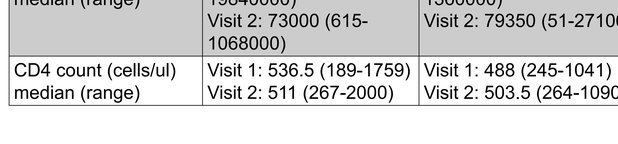
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BACKGROUND

Natural Killer (NK) cells are an important component of innate immunity that can modulate the pathogenesis of acute HIV-1 infection (AHI). However, the role of NK cells in mediating early host defense against infection with different HIV-1 subtypes, and clinical outcomes, remains poorly understood. Here, we studied the early imprinting effects of different HIV-1 subtypes and pro-inflammatory environment on the NK cell compartment in a unique cohort with AHI.

METHODS

Study cohort



Experimental procedure

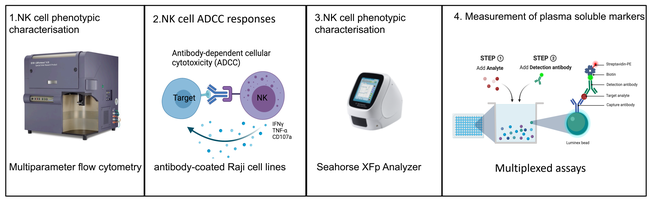


Fig. 1. Diagram for the study cohort and experimental procedures. A) Participants with AHI were sampled longitudinally in four different sub-Saharan African sites under "IAVI protocol C" (n=25 subtype A, n=17 subtype C, n=7 subtype D). Sample were collected in two-time points as indicated. **B)** Multiparameter flow cytometry was used for phenotypic characterisation. NK cell ADCC responses were determined against antibody coated Raji cells. The metabolic profile was assessed by a Seahorse technology. Plasma soluble markers were measured using multiplexed assays.

Table.1. Cohort characteristics.

	Subtype A	Subtype C,D, or R (non-A)
Age (Year) median (range)	28.5 (21-51)	31.5 (17-51)
Gender (Female:Male)	6:22	5:23
Country (Rwanda: Uganda: Kenya: Zambia)	(9:3:16:0)	(1:6:8:13)
Days post estimated date of infection	Visit 1: 32 (19-42) Visit 2: 95 (72-254)	Visit 1: 38 (24-42) Visit 2: 92 (81-117)
Viral Load (copies/ml) median (range)	Visit1: 83400 (612-19840000) Visit 2: 73000 (615-1068000)	Visit 1: 69646 (442-1360000) Visit 2: 79350 (51-2710682)
CD4 count (cells/ul) median (range)	Visit 1: 536.5 (189-1759) Visit 2: 511 (267-2000)	Visit 1: 488 (245-1041) Visit 2: 503.5 (264-1090)

RESULTS

Expansion of NK cell subsets with adaptive/memory features during AHI with subtype A compared to non-A characterized by lower expression of PLZF

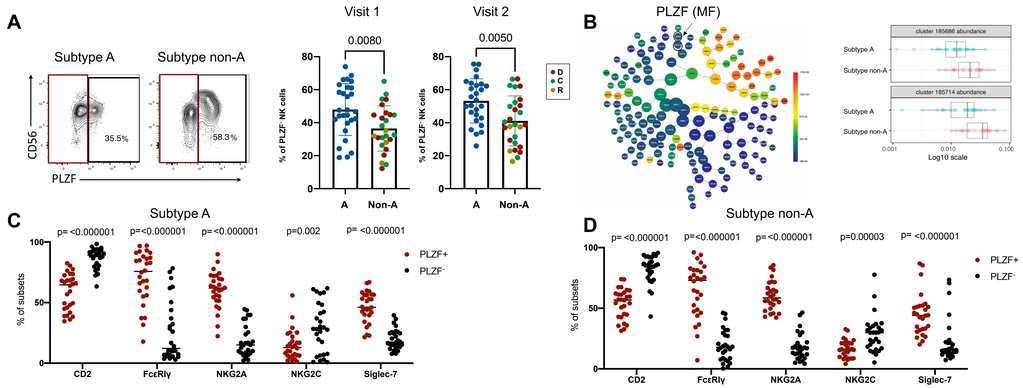


Fig. 1. NK cell characterization during AHI with different HIV-1 subtypes. A) Representative flow cytometric plots and summary data representing the frequency of PLZF$^-$ NK cells in HIV-positive individuals with subtype A (n=28) and non-A (n=28) infection. Error bars represent SD. **B)** Map of hierarchical clusters identified by Citrus. Black circles represent clusters of cells, whose cell abundances in the two groups are significantly different. The frequency of PLZF$^+$ (red circle) or PLZF$^-$ (black circle) NK cells expressing CD2, FcεRIγ, NKG2A, NKG2C, and Siglec-7 in subtype A **(C)** and non-A **(D)**.

Higher frequency of adaptive NK cells is associated with plasma levels of IL-2 and IL-12p70

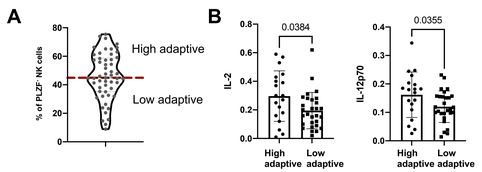


Fig. 2. Distinct biomarker signatures during AHI is linked with adaptive NK cell expansion. A) Summary plot representing the frequency of PLZF$^-$ NK cells in the cohort and threshold used to define low and high frequency of adaptive NK cells. **B)** Plasma levels of IL-2 and IL-12p70 in individuals with high or low frequency of adaptive NK cells during AHI.

NK cell ADCC capacity correlates inversely with HIV-1 viral load and reflects superior oxidative phosphorylation

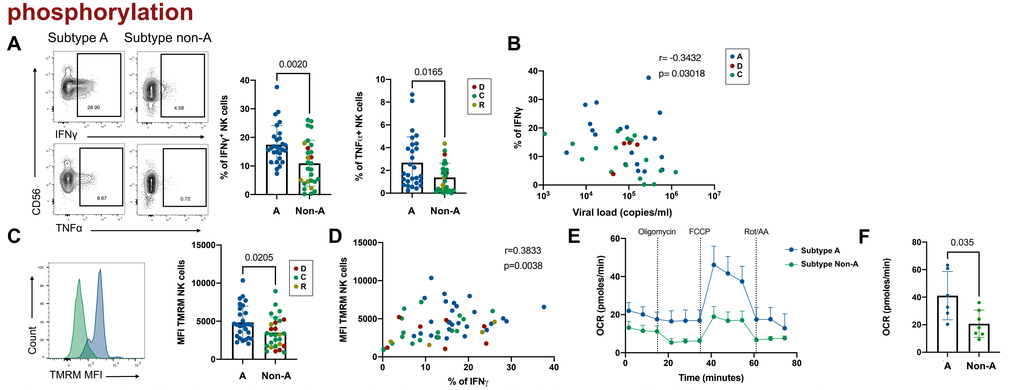


Fig. 3. Functional and metabolic characterization of NK cells during AHI with different HIV-1 subtypes. A) Representative flow cytometric plots and summary data representing the frequency of IFN-γ or TNFα-producing NK cells to antibody coated Raji cells in HIV-positive individuals with subtype A (n=28) and non-A (n=28) infection. Error bars represent SD. **B)** Correlation between the frequency of IFN-γ$^+$ NK cells and viral load**. C)** Histogram and summary data illustrating MFI of Tetramethylrhodamine methyl ester (TMRM) in NK cells. **D)** Correlation between TMRM MFI of NK cells and the frequency of IFNγ$^+$NK cells. **E)** Real-time analysis of oxygen consumption rate (OCR) in isolated NK cells from individuals with subtype A (n=6) and non-A (n=7) infection. **F)** Maximal oxidative phosphorylation capacity of NK cells in the study groups.

Increased frequency of adaptive NK cells is associated with lower HIV-1 viral load and higher CD4 T cell counts

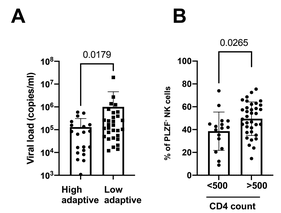


Fig. 4. Association between the frequency of adaptive NK cells and HIV-1 clinical parameters. A) Summary plot representing viral load in low and high adaptive NK cell groups. **B)** Frequency of PLZF$^-$ NK cells in individuals with CD4 T cell counts higher or lower than 500 cell/mm^3.

SUMMARY

- Adaptive NK cell subsets expand during AHI with subtype A compared to non-A.
- This adaptive NK cell signature was delineated by lower expression of the transcription factor PLZF and was further enriched by higher expression of the activating receptor NKG2C and lower expression of the signaling molecule FcεRγ [1] .
- Individuals with higher frequencies of adaptive NK cells have higher levels of IL-12p70 and IL-2.
- NK cells exhibit enhanced ADCC capacity, in particular IFN-γ production, and have superior metabolic profile in subtype A versus non-A.
- NK cell IFN-γ production correlates inversely with HIV-1 viral load.
- Individuals with higher frequency of adaptive NK cells have lower HIV-1 viral load higher CD4 counts (>500)

CONCLUSIONS

These data suggest that specific NK cell subsets could confer better HIV-1 control, highlighting their potential role as a prognostic marker and as a new target for the development of novel immunotherapeutic and 'cure' strategies.

REFERENCES

[1] Peppa et al. "Adaptive Reconfiguration of Natural Killer Cells in HIV-1 Infection." Frontiers in immunology vol. 9 474. 16 Mar. 2018.

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