IMPACT OF A NOVEL NATURAL KILLER CELL SUBSET ON IMMUNE RECONSTITUTION

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BACKGROUND

We have identified a novel subset of NK cells, called 'g-NK cells', which display adaptive immune features, including clonal-like expansion and long-term persistence[1,2,3]. The presence of g-NK cells is associated with previous infection by cytomegalovirus and have enhanced response to viral-infected cells in the presence of virus-specific antibodies[2,3]. We hypothesize that g-NK cells contribute to low CD4 counts and CD4 recovery during ART.

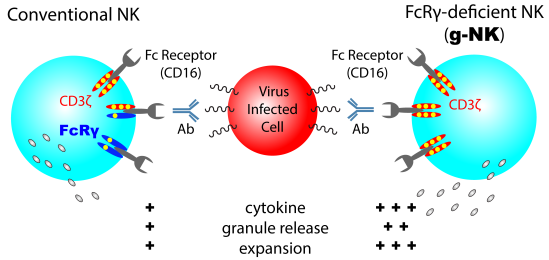


Figure 1. Schematic illustration of conventional NK and FcRγ-deficient (g-NK) cells. The Fc receptor for IgG (CD16) is associated with FcRγ (with 1 ITAM) and/or CD3ζ (with 3 ITAM) signaling adaptors as homodimers or heterodimers in conventional NK cells. However, CD16 is exclusively associated with CD3ζ in g-NK cells. Upon recognition of antibody-coated virus-infected cell, g-NK cells have greatly enhanced ability to produce cytokines, release cytotoxic granules and expand in number, compared to conventional NK cells.

METHOD

In a cohort of 18 MSM chronically infected HIV patients naïve to treatment before and 12 months after starting a PI-based cART, the presence of g-NK cells, as well as their frequencies and phenotypic characteristics, were measured by flow cytometry after intracellular staining of FcRγ signaling protein following cell surface marker staining. 17 HIV-negative control underwent identical procedures. Plasma biomarkers of inflammation were measured by ELISA and cytokine production by g-NK cells and conventional NK cells after stimulation with HIV-infected cells in the presence or absence of HIV-seropositive plasma.

RESULT

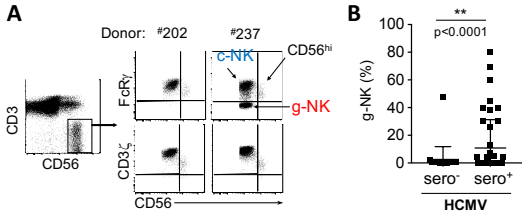


Figure 2. Identification of human g-NK cells and association with HCMV serology. (A) Dot plots show NK cell (CD56$^+$CD3$^-$CD14$^-$CD19$^-$) expression of FcRγ (*upper panels*) and CD3ζ (*lower panels*) from two representative donors. Conventional NK (c-NK) and g-NK cells are indicated. (B) The frequency of g-NK cells is presented for individual donor samples, which are grouped according to their serological status for IgG against HCMV.

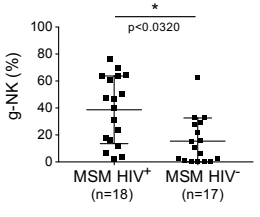


Figure 3. Higher frequencies of g-NK cells present in HIV-infected individuals. The frequency of g-NK cells is presented for individual MSM donors, which are grouped according to their HIV status.

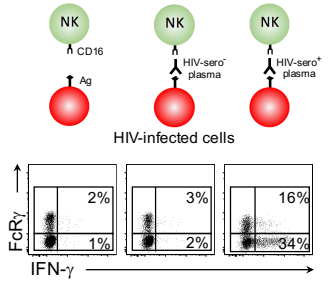


Figure 4. g-NK cells show enhanced cytokine production in response to HIV-infected cells in presence of HIV-sero$^+$ plasma. Dot plots show enhanced IFN-γ production by g-NK cells compared to conventional NK cells from a representative donor following incubation with HIV-infected cells in the absence or presence of indicated plasma. Numbers represent the relative percentage of IFN-γ$^+$ NK cells.

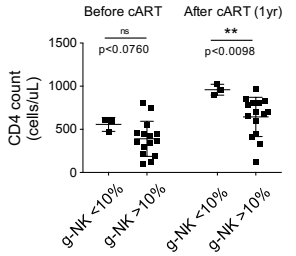


Figure 5. Higher frequencies of g-NK cells in HIV-infected individuals is associated with lower CD4 counts and recovery during ART. HIV$^+$ patients are grouped according to their frequencies of g-NK cells and CD4$^+$ cell counts before and after cART.

CONCLUSION

g-NK cells are more frequent in HIV+ pts compared to controls and may contribute to low CD4 counts in HIV patients and poor recovery during ART. g-NK cells may be a useful biomarker for predicting how the CD4$^+$ T cell population may recover during HIV treatment.

REFERENCE

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