

Natural Killer Cells as Target for Immune-Based Intervention in HIV Disease

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1. Background

NK cells play an important role in innate immune control of HIV infection and disease progression. To assess the contribution of NK cells as target for immunotherapy in HIV infection, we evaluated the priming effect of IL-15 on human peripheral NK cells, from viremic and aviremic HIV-infected patients, measuring the production of IFN- γ , CCL4 and CCL5 chemokines and the expression of surface CD69 molecule.

2. Methods

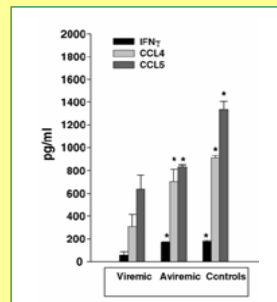
Study population consisted of:

PATIENTS	N°	CD4	HIV-RNA	Months of HAART
HAART naïve	13	65	4,7 log	-
Aviremic HAART	27	673.2	NR	12-36
Healthy Donors	16			

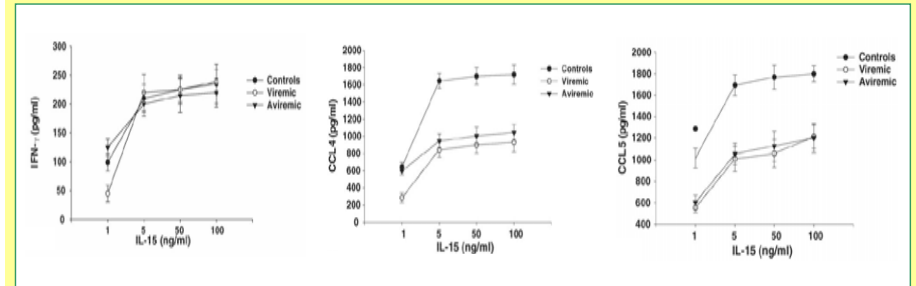
NK cells were isolated by negative selection from peripheral PBMC (NK cell negative isolation kit, Dynal Biotech) with a purity >90% and cultured for 24 hrs with medium alone or in presence of IL-15 (100U/ml), IL-2 (100U/ml), IL-15+IL-12, and IL-2+IL-12. IFN- γ and CC chemokines were measured in culture supernatant and cell surface CD69 expression was evaluated in CD3-/CD16+/CD56+ gates.

3. Results

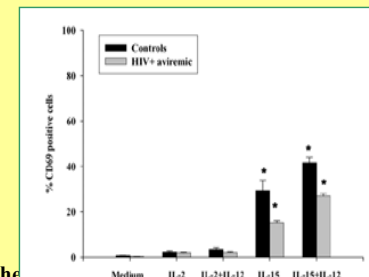
The production of IFN- γ , CCL4 and CCL5 by NK cells from antiretroviral-naïve viremic patients was significantly smaller than quantity found in aviremic HAART-treated patients and healthy controls ($p < 0.05$).



In vitro IL-15 priming induced a significant increase of IFN- γ , CCL4 and CCL5 production in both viremic and aviremic patients. The dose-response curve showed that increased release of INF- γ and CC chemokines was found at IL-15 concentrations of 10 to 100 ng/ml.



NK cells from healthy donors and aviremic HAART-treated patients stimulated with IL-15 alone or IL-15 plus IL-12 showed the highest and most significant increase both in the percentage of CD69 expressing cells and in mean fluorescence intensity; little or no activation was observed in NK cells treated with IL-2 or IL-2 plus IL-12.



The greatest levels of CC chemokines were found in the culture supernatants from NK cells treated with the combination of IL-15 plus IL-12, while no effect was detected with IL-2 alone or IL-2 plus IL-12.

4. Discussion

NK cells derived from HIV viremic and aviremic patients are capable of secreting relevant amounts of IFN- γ and CC chemokine after *in vitro* treatment with IL-15 alone or in combination with IL-12.

The present study indicates that NK cells are an important target for immunotherapeutic agents and provides additional pre-clinical data supporting the great potential of IL-15 in the immune-based interventions in HIV disease.