NK cells are preserved by early ART in HIV-infected children with lower reservoir

Sonia Zicari¹, Margherita Doria¹, Sara Domínguez-Rodríguez², Nicola Cotugno³, Alfredo Tagarro³, Pablo Rojo Conejo³, Eleni Nastouli⁵, Kathleen Gartner⁵, Nigel Klein⁶, Caroline Foster⁵, Savita Pahwa⁶, Anita De Rossi⁵, Carlo Giaquinto⁵, Paolo Rossi⁵, Paolo Palma⁵, for the EPIICAL consortium

¹Bambino Gesù Children’s Hospital, Rome, Italy, ²Hospital Universitario 12 de Octubre, Madrid, Spain, ³Great Ormond Street NHS Foundation Trust, London, UK, ⁴London School of Hygiene & Tropical Medicine, London, UK, ⁵Imperial College Healthcare NHS Trust, London, UK, ⁶University of Miami Miller School of Medicine, Miami, FL, USA

University of Padova, Padova, Italy

Background

HIV infection causes pathological changes in the natural killer (NK) cell compartment that can be only partially restored by antiretroviral therapy (ART). We studied NK cells phenotype and function in perinatally HIV-infected children (PHIV) enrolled in a multicenter cross-sectional study (CARMA, EPIICAL consortium), who started ART at different ages (early treated, ET ≤ 6 months; late treated, LT > 6 months to 2 years).

Methods

40 PHIV who started ART< 2 years of life and had undetectable viremia (< 50 HIV copies/mL) for at least 5 years, were enrolled in 7 European research centers. HIV-1 DNA copies/10⁶ PBMCs were measured by real-time PCR. NK cells were analyzed by flow cytometry for % of CD56dim, CD56bright, CD56neg subsets, receptor expression, maturation profile, degranulation capacity (CD107a expression) in the presence or not of K562 cells, and IFNγ production after stimulation or not with a cocktail of cytokines. Data were analyzed by Spearman correlation plots and multivariable Poisson regression model (adjusted for baseline %CD4 and RNA HIV viral load and for age at ART start as interaction term, either ET or LT) to explore the association between NK cell parameters and HIV reservoir modulated by age at ART start.

Gating strategy

Results

Later treatment in PHIV leads to a shift of NK cells to the anergic CD56neg subset that is associated with an increase of HIV reservoir size. For each 1% increase in %CD56neg, 3% upregulation of HIV reservoir is found and this effect is reduced in ET. LT display a persistent “activated” phenotype (i.e. NKP46+, NKG2D+, high Perforin expression) that is not present in ET; for each 1-unit increase in % of NKG2D+, % of NKP46+ or Perforin mean fluorescence intensity, there is an enrichment of 1%, 4% or 0.01% in HIV reservoir, respectively.

Moreover, %CD107a+ and %IFNγ+ non-stimulated NK cells show a positive association with HIV DNA, and these effects are decreased in ET. Finally, among CD56neg cells, the frequencies of early differentiated and mature cells are associated with HIV DNA in a positive and inverse manner, respectively; whereas these effects were lower in ET.

Conclusions

Our results demonstrate that starting ART as soon as possible in PHIV is important to preserve NK cell features. Notably, we show for the first time that a preserved NK cell compartment in PHIV is associated with lower HIV viral reservoir.

*The EPIICAL consortium

Author contact information: sonia.zicari@opbg.net