A Skewed NK Cell Repertoire Persists in People with HIV-1 Despite Long-Term ART


1Department of Infectious Diseases and Microbiology, University of Pittsburgh School of Public Health, 2Department of Medicine, University of Pittsburgh School of Medicine, 3Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, 4Department of Medicine, Weill Cornell Medicine, 5Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill, 6Infectious Disease Division, Massachusetts General Hospital, Harvard Medical School

Background

• HIV-1 infection greatly alters the NK cell phenotypic and functional repertoire
• This is highlighted by the expansion of a rare population of FcRγ− NK cells exhibiting characteristics of traditional immunologic memory in people with HIV (PWH)
• NK cell subset distribution and function are also sequentially deregulated with chronic HIV-1 viremia
• On average, 24 months of suppressive antiretroviral therapy (ART) are required before normalization of surface expression of CD56 and NKGA and recovery in functionality
• PWH on effective ART continue to show signs of residual immune dysfunction, including persistence of NK cell activation
• Do chronic HIV-1 infection and long-term ART have enduring effects on conventional and memory-like NK cells?

Methods

• Longitudinal analysis detailing conventional and memory-like NK cell characteristics in PWH (n=60) of the AIDS Clinical Trials Group (ACTG) cohort study A5321
• All participants initiated ART in ACTG trials during chronic infection and had well-documented consistent HIV-1 suppression
• Phenotypic and functional NK cell profiles, as well as frequencies of FcRγ− NK cells, were determined by flow cytometry at 4 weeks, 1 year, and 4 years post-initiation of ART
• Single-cell multiomic analysis was performed using the BD Rhapsody® Express Single-Cell Analysis System

Results

Phenotypic differences of FcRγ− and FcRγ+ NK cells do not diminish in response to ART

- Evaluation by flow cytometry of FMC64 from PWH of the ACTG A5321 study with or without ART: NK cell frequency (%: TP1, TP2, TP4, and TP6) increased in FcRγ− and decreased in FcRγ+ at 4 years of ART compared to baseline at 1 year of ART; however, statistical significance was not reached in either group. FcRγ− (B) and FcRγ+ (D) NK cells were determined by flow cytometry at 4 weeks, 1 year, and 4 years post-initiation of ART.

Persistence of reduced IL-18 responsiveness in the FcRγ− population

- Evaluation by flow cytometry of FMC64, baseline and 4 years of suppressive ART in PWH, with or without ART: NK cell frequency (%: TP1, TP2, TP4, and TP6) increased in FcRγ− and decreased in FcRγ+ at 4 years of ART compared to baseline at 1 year of ART; however, statistical significance was not reached in either group. FcRγ− (B) and FcRγ+ (D) NK cells were determined by flow cytometry at 4 weeks, 1 year, and 4 years post-initiation of ART.

An abnormal NK cell subset distribution in HIV-1 infection

- Evaluation by flow cytometry of FMC64, baseline and 4 years of suppressive ART in PWH, with or without ART: NK cell frequency (%: TP1, TP2, TP4, and TP6) increased in FcRγ− and decreased in FcRγ+ at 4 years of ART compared to baseline at 1 year of ART; however, statistical significance was not reached in either group. FcRγ− (B) and FcRγ+ (D) NK cells were determined by flow cytometry at 4 weeks, 1 year, and 4 years post-initiation of ART.

Conclusions

• NK cells progress along a spectrum of differentiation in PWH on long-term ART
• Conventional but not FcRγ− NK cell downregulate KLRG1 upon IL-18+12-16 exposure
• PWH display atypical NK cell subsets, representing intermediate stages of NK-poiinesses
• NK cell irregularities persist in PWH despite long-term ART, underscoring the need to better understand the causative mechanisms that prevent full restoration of immune health in PWH

Contact Information:
Renee Anderko | anderkor@pitt.edu