



Karolinska Institutet

Centrum för Infektionsmedicin
Institutionen för Medicin, Huddinge

Role of Cellular Immune Functions through the Course of HIV-1 Natural Infection in Ugandans

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av

Michael A. Eller

Huvudhandledare
Docent Johan K. Sandberg, PhD
Centrum för Infektionsmedicin
Institutionen för Medicin, Huddinge
Karolinska Institutet

Bihandledare:
Jeffrey R. Currier, PhD
US Military HIV Research Program

Bihandledare:
Professor Fred Wabwire-Mangen, MD, MPH, PhD
School of Public Health
Makerere University

Bihandledare:
Merlin L. Robb, MD
US Military HIV Research Program

Fakultetsopponent:
Professor Sarah Rowland-Jones
University of Oxford
The Weatherall Institute of Molecular Medicine

Betygsnämnd:
Docent Louise Berg
Enheten för Reumatologi
Institutionen för Medicin, Solna
Karolinska Institutet

Professor Jan Albert
Institutionen för Mikrobiologi, Tumör- och Cellbiologi
Karolinska Institutet

Professor Marita Troye-Blomberg
Wenner-Gren Institute for Experimental Biology
Stockholms Universitet

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ABSTRACT

HIV-1 infection remains a major crisis in sub-Saharan Africa and more information about disease pathogenesis and immune correlates of protection are needed. Uganda, with a population of approximately 33 million people, has a national HIV-1 prevalence over 6% with subtype A and subtype D predominating. We aimed to characterize immune cell functions in Ugandans with untreated chronic HIV-1 infection, and identify aspects of the immune response that are associated with control of viremia and disease progression. As this work was based on stored specimens from cohorts in the rural districts of Kayunga and Rakai, we first detailed the importance of rigorous protocols for quality PBMC cryopreservation in the resource limited setting in **Paper I**. Importantly, cryopreservation did not compromise relative frequencies or function of PBMCs, and long-term storage of samples for greater than 3 years did not impact yield or viability. We developed a program to monitor PBMC processing to ensure suitability for the studies of adaptive and innate immunity included in this thesis. In **Paper II**, we found redistribution of NK cell subsets, with increase in CD56^{neg} NK cells and reduction of CD56^{dim} NK cells, in HIV-1 infected Ugandans. Moreover, we observed decreased NK cell expression of KIR2DL1, NKG2A, CD161 and NKp30 in these patients. Interestingly, severe loss of CD4 T cells was associated with elevated levels of KIR expression and degranulation in CD56^{bright} NK cells, suggesting that cytotoxic function develops in this subset in progressive HIV disease. In **Paper IV**, we continued to build on these findings and discovered a preferential expansion of KIR3DL1+ NK cells that was directly proportional to HIV-1 viral load in donors that possessed the HLA-B Bw4-80I motif. Other inhibitory KIRs were reduced or remained constant in the presence of their HLA ligands. Overall, NK cells in HIV-1 infected Ugandans displayed an elevated activity despite an altered functional and phenotypic profile in chronic disease. Additionally, NK cells in these patients were more polyfunctional with regard to CD107a, IFN- γ , and MIP-1 β expression as compared to uninfected controls. The KIR3DL1+ NK cells in Bw4+ individuals were particularly responsive, producing increased IFN- γ and MIP-1 β . In **Paper III**, we examined T cell activation in HIV-1 infected Ugandans, in an effort to better define the phenotypic aspects unique to progressive infection and understand the mechanisms behind disease progression. We found that activated CD4 T cells displayed a deregulated effector memory (T_{DEM}) phenotype and levels of such cells were directly proportional to HIV-1 viral load. Individuals with elevated frequencies of CD4 T_{DEM} cells progressed faster to AIDS. These CD4 T_{DEM} cells correlated with markers of microbial translocation and innate immune activation such as sCD14 and IL-6. *In vitro* assays revealed that CD4 T_{DEM} cells displayed a diverse TCR V β repertoire, and could be driven by a diverse array of pathogens including HIV-1 itself. Taken together, the CD4 T_{DEM} cell data supports a model where innate immune activation and chronic antigen stimulation are involved in pathological T cell activation and HIV-1 disease progression. In summary, these Ugandan cohort studies have provided insight into the balance between healthy immune responses and pathological immune activation that characterizes HIV-1 infection. More targeted studies are needed in order to develop therapeutic and preventative strategies that may alleviate the burden of HIV-1.