Role of Monocytes, CTL and NK cells in primary HTLV-1 infection

Moles R[1], Sarkis S[1], Galli V[1], Omsland M[1], Artesi M[2,3], Bissa M[1], McKinnon K[4], Brown S[4], Hahaut V [2,3], Washington-Parks R[1], Welsh J[5], Venzon DJ, Gutowska A[1], Doster M[1], Breed MW[7], Killoran KE[7], Kramer J[7], Jones J[5], Moniuszko M[8], Van den Broeke A [2,3], Pise-Masison CA[1], and Franchini G[1]

[1] Animal Models and Retroviral Vaccines Section, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA;
[2] Laboratory of Experimental Hematology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium;
[3] Unit of Animal Genomics, GIGA, Université de Liège, Liège, Belgium;
[4] Vaccine Branch Flow Cytometry Core, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA;
[5] Translational Nanobiology Section, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA;
[6] Biostatistics and Data Management Section, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA;
[7] Laboratory Animal Sciences Program, Leidos Biomedical Research Inc., Frederick National Laboratory, Frederick, Maryland, USA;
[8] Department of Allergology and Internal Medicine, Medical University of Bialystok, Bialystok, Poland.

Background: The immune cells that inhibit or favor early Human T-cell Leukemia Virus Type 1 (HTLV-1) infection are still unknown, and their identification is critical for understanding viral pathogenesis and for the development of an effective vaccine.

Methods: We investigated the impact of monocytes, Natural Killer (NK) cells, and CD8+ T-cells in primary HTLV-1 infection. We depleted these cellular subsets in macaques prior to inoculation of either HTLV-1 wild type ($HTLV\text{-}1_{WT}$) or $HTLV\text{-}1_{p12KO}$, a mutant unable to express the viral proteins encoded by the *open reading frame I* (*orf-I)*.

Results: Double NK and CD8+ T-cells or CD8+ depletion alone accelerated seroconversion in all animals exposed to $HTLV\text{-}1_{WT}$. Importantly, the lack of infectivity of the $HTLV\text{-}1_{p12KO}$ virus was fully restored only when NK and CD8+ cells were depleted. Monocyte/macrophage depletion resulted in accelerated seroconversion in all animals exposed to $HTLV\text{-}1_{WT}$, but antibody titers to the virus were low and unsustained. In contrast, only 20% of deleted animals exposed to $HTLV\text{-}1_{p12KO}$ seroconverted.
We also characterized the role of the *orf-I* on monocytes` function. Our results demonstrated that *orf-I* expression is associated with inhibiting inflammasome activation in primary cells. Moreover, we showed that *orf-I* expression increases CD47 “don’t-eat-me signal” surface expression in infected cells, resulting in evasion of monocyte engulfment.

Conclusion: Our data demonstrate a critical role of NK cells in restricting early infection, suggesting that a preventive vaccine needs to induce innate responses. Furthermore,

our study revealed a dual role of monocytes in primary infection. On one hand, *orf-I* expression increases the chances of viral transmission by sparing infected cells from phagocytic clearance, and on the other may protect the engulfed infected cells by modulating inflammasome activation. Collectively, these data indicate that, once the infection is established, the stoichiometry of *orf-I* expression may contribute to the chronic inflammation observed in patients by evading monocyte engulfment.

Disclosure of interest: None