HTLV-1c infection and pulmonary disease is defined by chronic T-cell activation and high expression of TIM-3

Authors:
Hirons A[1], Hirons N[2], Burmas L[1], Ellenberg P[1], Yap AHY[1], Sijmons D[1], Collins S[1], Talukder MR[3], Vickas AH[4], Selva KJ[1], Grimley SL[1], Chung AW[1], Khoury G[1], Einsiedel L[1,5], Juno JA[1], Purcell DFJ[1]

[1] Department of Microbiology and Immunology at the Peter Doherty Institute for Infection and Immunity, University of Melbourne, Victoria, Australia, [2] University of Melbourne, Victoria, Australia, [3] Baker Institute, Alice Springs, Northern Territory, Australia, [4] Charles Darwin University, Northern Territory, Australia, [5] Department of Medicine, Alice Springs Hospital, Northern Territory, Australia

Background:
The high prevalence of Human T-cell lymphotropic virus type-1 subtype-C (HTLV-1c) infection and HTLV-1-associated pulmonary disease (HAPD) in Central Australia, coupled with poorer overall heath and early mortality for people living with HTLV-1c, prompted an investigation surrounding the host immunological response and factors contributing to these outcomes.

Methods:
PBMCs and plasma were collected from a hospital-based Central Australian cohort (n=95). Plasma cytokines and soluble T-cell markers were measured by bead-based immunoassay and PBMC proviral load (PVL) by droplet digital PCR. HTLV-1c-specific T-cell responses were determined by stimulating PBMCs with peptide libraries and ex vivo T-cell phenotyping by flow cytometry.

Results:
We determined a plasma cytokine signature in HTLV-1c infection with hallmarks of both inflammation and immunomodulation. CD4 circulating T-follicular helper (cTFH) and memory T (Tmem) populations were expanded and chronically activated in HTLV-1c+ donors, correlating to PVL. The Tax-cTFH and T-helper 17 (Th17) responses were more prominent in HAPD- donors than HAPD+, while the frequency of Env-specific Tmem correlated to PVL. The Tax-CD8 response was more robust in HAPD- participants compared to HAPD+.

We characterised three discrete populations of CD4 effector/memory (TEM) associated with HTLV-1c infection: senescent $CD57^{+}$, chronically activated $CD57^{-}$ $HLA\text{-}DR^{+}CD38^{+}$ and a novel population of $CD57^{-}HLA\text{-}DR^{-}CD38^{+}TIM\text{-}3^{+}$. These phenotypes had frequent co-expression of exhaustion markers T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), programmed cell death protein-1 (PD-1), and T-cell immunoreceptor with immunoglobulin and ITINM domain (TIGIT). Similarly, CD8 TEM cells displayed chronic activation and TIM-3+ expression in HTLV-1c+ donors, while Granzyme-B was downregulated. Soluble TIM-3 was higher in HTLV-1c+ plasma compared to controls.

Conclusion:

We characterised HTLV-1c-specific responses that may correlate with disease protection. Strikingly, we found chronic T-cell activation was prominent in HTLV-1c infection and HAPD, and displayed hallmarks of exhaustion.

Disclosure of Interest Statement:
None