Immune activation and dysfunction are defining characteristics of every HTLV-1c infection

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Background:
HTLV-1 subtype-C (HTLV-1c) infection is endemic in parts of Australia and Melanesia, with prevalence rates of over 40% in remote central Australian First Nations communities. HTLV-1c infection is commonly associated with inflammatory diseases such as bronchiectasis (Bex). This study aims to explore the relationship between the host and virus and determine what might be contributing to HTLV-1c related pathologies observed in Australia.

Methods:
Whole blood was collected from donors in Alice Springs Hospital. Plasma cytokine levels (n=77) were analysed with the Milliplex assay on the Luminex platform and correlated with clinical data and proviral load (PVL) measured via ddPCR. HTLV-1c-specific CD4+ and CD8+ T-cell responses (n=20) were measured by flow cytometry following stimulation with overlapping Tax and Env-peptides. CD4+ T-cell phenotypes (n=29) were analysed for expansion. Amplification of single integrated proviruses was achieved by limiting dilution touchdown nested PCR (n=6) and were sequenced using the Oxford Nanopore platform.

Results:
TNF-α and Log_{10}(IP-10) levels were significantly higher in all HTLV-1c+ donors when compared to HTLV-1c- donors from similar background. Principal component analysis (PCA), partial least squares discriminant analysis (PLS-DA) and logistic regression modelling showed these cytokines, along with MCP-1, IL-10 and IL-2 as indicators of HTLV-1c infection. Our data revealed a 10-fold increase in PVL equates a 3.6-fold increase in the odds of exhibiting bronchiectasis.

Notably, we observed a significant expansion of activated CD4+ T-cells (HLA-DR+CD38+) and phenotypic lung homing cells in the effector memory subset in asymptomatic carriers (ACs) and Bex donors when compared to HTLV-1c- and healthy donors, which positively correlated with the PVL of HTLV-1c+ donors.

Moreover, we found HTLV-1c provirus is most highly enriched in CCR4+ cells, both T reg and lung homing phenotypes, and these reservoirs contain >80% defective provirus. Interestingly, CCR4-CD4+ T-cells were enriched in full-length HTLV-1c provirus.

Conclusion:

Altogether, our study reveals significant chronic immune activation of T-cells in every HTLV-1c infected person and a complex host-virus interplay that provides a focus for future studies assessing new therapeutic strategies.

Disclosure of Interest Statement:
The authors declare no competing financial interests in the development of this study.