Pulmonary disease in HTLV-1c infection is characterised by lung-homing T-cells with defective provirus retaining *hbz*

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Background: Human T-cell lymphotropic virus type-1 (HTLV-1) integrates into host DNA resulting in life-long infection that underlies malignancy, inflammatory disease, and early all-cause mortality. HTLV-1 subtype-C endures as an endemic infection in Central Australia and is associated with pulmonary disease. The cellular and viral features driving HTLV-1c pathogenesis remain poorly understood.

Methods: We recruited 36 First Nations participants from Alice Springs Hospital in Central Australia. We analysed plasma biomarker sVCAM1 and three circulating CD4+ T-cell phenotypes by flow cytometry: Lung-homing (T_{LH}, CCR4+CD49d+Integrinβ7-), regulatory T-cells (T_{REG}, CCR4+CD49d-CD127-) and CCR4- (T_{CCR4-}). We determined proviral load by ddPCR. Haplotype-resolved proviruses were assembled from 6 donors using single provirus amplification and long-read sequencing (SPA-ONT-seq).

Results: All HTLV-1c+ participants showed expansion of chronically activated T_{LH}cells. These cells were highly infected with HTLV-1c provirus and enriched in lung tissue of humanised mice, confirming pulmonary trafficking. Despite extensive structural diversity in the proviral landscape, defective proviruses in participants with pulmonary disease preferentially retain virulence factor hbz. Defective proviruses were detected in sputum of HTLV-1c+ participants. We discovered chimeric HTLV-1c:human proviruses containing internalised host DNA segments and implicated them in modulating host gene expression.

Conclusion: HTLV-1c mediates pulmonary disease through lung-homing of chronically activated CD4+ T-cells harbouring defective proviruses that retain hbz. CD49d and hbz represent promising therapeutic targets. Single-provirus sequencing revealed previously unrecognized structural complexity, including functional viral-host chimeras, with implications for HTLV-1 pathogenesis

Disclosure of Interest Statement:
The authors have no conflicts of interest to disclose