The helicase-like transcription factor inhibits infectious replication of human T-cell leukemia virus type 1

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Background:
Transcriptomic data indicate that expression of the helicase-like transcription factor (HLTF) is downregulated in T-cells of ATL patients. HLTF is a transcription factor having E3 ubiquitin ligase activity. The objective of this project is to investigate the role of HLTF on HTLV-1 infectivity.

Methods:
Transcription and translation of HLTF were analyzed in cell lines derived from HTLV-1-infected subjects using RT-qPCR, immunoblots, chromatin immunoprecipitation and flow cytometry. Protein interactions were evaluated by co-immunoprecipitations and Gaussia princeps complementation assays. The impact of HLTF on HTLV-1 infectivity was evaluated in co-cultures of HTLV-1-infected lymphocytes with Jurkat cells transduced with a LTR-luciferase reporter. HLTF expression was modulated by gene transduction. The role of HLTF on NF-kB activation was determined by luciferase-based reporter assays. Intracellular trafficking through the Golgi apparatus was assessed by confocal and electron microscopy.

Results:
Data show that Tax inhibits HLTF transcription via the H3K27 methyltransferase EZH2 of the Polycomb repressive complex 2. The Tax protein directly interacts with HLTF and induces its proteasomal degradation. Co-culture experiments demonstrate that HLTF transduction decreases HTLV-1 infectivity. HLTF is a thus restriction factor against HTLV-1 and interferes with the ability of infected cells to transmit the virus to new cells. Electron microscopy reveals that HLTF transduction fragments the Golgi apparatus and increases the number of secretory granules. Luciferase-based reporter assays show that HLTF transduction synergizes with Tax to induce NF-kB activation. As a consequence, HLTF transduction increases the number of immature virions.

Conclusion:
Data demonstrate that HLTF is a restriction factor that reduces HTLV-1 infectivity. By disturbing the Golgi apparatus and the NF-kB pathway, HLTF leads to defective HTLV-1 particles unable to infect new cells. HLTF is thus a unique example of a restriction factor that impairs production of mature virions by boosting intracellular trafficking through the Golgi apparatus.

Disclosure of Interest Statement: none