In vivo antagonistic role of the Human T-Cell Leukemia Virus Type 1 regulatory proteins Tax and HBZ

Abdou Akkouche1,2, Sara Moodad1,2, Rita Hleihel1,2, Hala Skayneh1,2, Severine Chambeyron3, Hiba El Hajj4*, Ali Bazarbachi1,2*

1 Department of Internal Medicine, Faculty of Medicine, American University of Beirut, Lebanon
2 Department of Anatomy, Cell Biology and Physiological Sciences, American University of Beirut, Lebanon
3 Institute of Human Genetics, CNRS, UMR 9002, Montpellier University, France
4 Department of Experimental Pathology, Immunology and Microbiology, Faculty of Medicine, American University of Beirut, Lebanon

Background:

Adult T cell leukemia (ATL) is an aggressive malignancy secondary to chronic infection with the human T-cell leukemia virus type 1 (HTLV-1) infection. Two viral proteins, Tax and HBZ, play central roles in ATL leukemogenesis. Tax expression transforms T cells in vitro and induces ATL in mice. Tax also induces a rough eye phenotype and increases hemocyte count in Drosophila melanogaster, indicative of transformation. Among multiple functions, Tax modulates the expression of the enhancer of zeste homolog 2 (EZH2), a methyltransferase of the Polycomb Repressive Complex 2 (PRC2), leading to H3K27me3-dependent reprogramming of around half of cellular genes.

Objectives:

Tax activates the NF-κB pathway and modulates the epigenetic machinery to induce cellular proliferation and malignant transformation. HBZ is a negative regulator of Tax-mediated viral transcription. HBZ effects on epigenetic signatures are underexplored. We investigated the antagonistic role of HBZ on Tax in vivo, and explored HBZ-mediated epigenetic changes.

Methods:

We generated hbz or tax/hbz transgenic flies and explored the phenotypes and epigenetic changes in vivo. We also used Relish-RNAi, E(z)-RNAi, SUZ12-RNAi to investigate the effect of Tax, HBZ, or Tax/HBZ dual expression on NF-κB pathway, and PRC2-epigenetic regulation in vivo.

Results:

We demonstrated that, unlike Tax, which induces NF-κB activation and enhances PRC2 activity, HBZ neither induces transformation nor NF-κB activation in vivo. Overexpression of Tax or HBZ increases the PRC2 activity and both proteins directly
interact with PRC2 complex core components. Importantly, overexpression of HBZ in tax transgenic flies prevents Tax-induced NF-κB or PRC2 activation and totally rescues Tax-induced transformation resulting in inhibition of malignant cellular proliferation and its consequent senescence.

Conclusion:

Our results establish the in vivo antagonistic effect of HBZ on Tax-induced transformation and cellular effects. This study helps understanding long-term HTLV-1 persistence and cellular transformation providing further understanding on ATL pathogenesis and opening perspectives for new therapeutic strategies targeting the epigenetic machinery in ATL.

Disclosure of Interest Statement:
Nothing to disclose.

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