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

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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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