



POSTER PRESENTATION

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HTLV-1 Tax disrupts the host epigenome by interacting with a Polycomb group protein EZH2

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ATL is a highly aggressive T-cell neoplasm caused by HTLV-1. We have recently demonstrated that EZH2, a catalytic enzyme of histone H3K27 methylation, is over-expressed in ATL cells, which contributes to persistent NF- κ B activation by repressing a tumor-suppressive miRNA, miR-31. This suggests that epigenetic abnormalities are closely associated with the molecular hallmarks of leukemic cells. However, the mechanisms by which epigenetic disruption is caused and sustained in HTLV-1 infected cells remain to be clarified. In the present study, we first found that Tax directly interacts with EZH2 in HTLV-1 infected cells. Given that epigenetic state is directly affected by cell lineage-dependent transcription factors and genetic background, we assessed the functional interconnection between HTLV-1 Tax and the histone methyltransferases in an appropriate model. Using a lentivirus vector, we introduced *tax* gene into peripheral blood mononuclear cells (PBMCs) and CD4⁺ T-cells from healthy donors and established Tax-transduced T-cells. In this model, we observed overexpression of EZH2, aberrant accumulation of H3K27 trimethylation, and epigenetic silencing of *p21^{cip1/waf1}*, all of which have been observed in primary ATL cells. In addition, EZH2 inhibition reduced the viability of Tax-transduced T-cells. Our results strongly suggest that Tax epigenetically affects gene expression through its interaction with EZH2, and that Tax-dependent epigenetic abnormalities may be involved in determining the molecular characteristics of HTLV-1-infected cells as well as ATL cells. Since epigenetic marks are potentially reversible, development of genuine epigenetic-targeted drugs will hold great promise in treatment of HTLV-1-related diseases.

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