



POSTER PRESENTATION

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# Metformin inhibits human T-cell leukemia virus type 1 transcription through activation of LKB1 and salt-inducible kinases

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Human T-cell leukemia virus type 1 (HTLV-1) causes adult T-cell leukemia (ATL). Specific therapeutic and prophylactic agents are not available. Epidemiological studies have established a correlation between long-term use of the commonly prescribed anti-diabetic drug metformin and a decrease in the incidence of breast and other cancers. Whether metformin might also have anti-HTLV-1 and anti-ATL activity is unclear. In this study we demonstrate an inhibitory effect of metformin on HTLV-1 transcription mediated through the activation of LKB1 tumor suppressor and downstream salt-inducible kinases (SIKs). Treatment of HTLV-1-transformed ATL cells or cells transfected with HTLV-1 molecular clone pX1MT with metformin led to reduction in cell-free virion production and inhibition of cell proliferation. This effect was attributed to the activation of LKB1/SIK1 which compromised Tax expression and HTLV-1 transcription. LKB1 and SIKs function as host restriction factors that counteract Tax activation of HTLV-1 long terminal repeats. Expression of LKB1 and activated SIKs effectively blunted Tax activity in a phosphorylation-dependent manner in LKB1-null HeLa cells, whereas compromising these kinases, but not AMP-dependent protein kinases, augmented Tax function in LKB1-proficient HEK293T cells. Activated LKB1 and SIKs associated with Tax. Enforced expression of LKB1 or SIK1 in pX1MT-transfected cells and HTLV-1-transformed ATL cells repressed proviral transcription, whereas depletion of LKB1 boosted Tax expression. Taken together, our findings revealed a potential

therapeutic and prophylactic agent for ATL as well as a new negative regulatory function of LKB1 and SIKs in HTLV-1 transcription. (Supported by HKU7661/08M, HKU7674/12M, HKU1/CRF/11G and SKY-MRF-2011).

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