Host-virus interactions: HTLV antisense regulatory proteins play a role in the dysregulation of NF-κB pathway

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Human T-cell leukemia virus type 1 (HTLV-1) is the causative agent of adult T-cell leukemia (ATL), an aggressive form of T-cell malignancy with no cure. The HTLV-1 oncoprotein Tax plays a key role in CD4+ T-cell transformation, mainly through constitutive activation of both the canonical and the alternative NF-κB pathways. The HTLV-1 basic zipper protein (HBZ), encoded by the antisense viral genome strand, plays an essential role in the oncogenic process in concert with Tax, mediating T-cell proliferation. Unlike HTLV-1, the genetically related retrovirus HTLV-2 is not associated with ATL diseases. Functional comparisons between HTLV-1 regulatory proteins, Tax-1 and HBZ, and the HTLV-2 homologs, Tax-2 and APH-2, may highlight different mechanisms of their oncogenic potential. The aim of this study is to investigate how the antisense proteins HBZ and APH-2 impaired the NF-κB pathway activation. We found that both HBZ and APH-2 antagonized the NF-κB promoter activity mediated by Tax, but not in the same extent. Analyzing the intracellular distribution of the antisense proteins, we found that APH-2 is retained in cytoplasm complexes, whereas HBZ is mainly distributed into the nucleus. We observed that in presence of APH-2 and Tax-2, the degradation of the IκB-α inhibitor was reduced. Moreover, we found that unlike HBZ, APH-2 formed complexes with an upstream inhibitor of the alternative NF-κB pathway, the TNF receptor-associated factor 3, TRAF3. We generated a TRAF3 knock-out cell line applying the CRISPR/Cas9-mediated genome editing. By luciferase assays, we showed that TRAF3 is not required for Tax mediated NF-κB promoter activation. Analyses are in progress to test the inhibitory effect of the antisense HBZ and APH-2 proteins on NF-κB promoter activity in absence of TRAF3. The results of this study may contribute to clarify the effect of the alternative NF-κB viral deregulation pathway in the expression of proinflammatory genes.