

## HTLV-1 BASIC LEUCIN ZIPPER FACTOR AND ITS HOMOLOGOUS APH-2 IMPAIR NF- $\kappa$ B ACTIVATION MEDIATED BY THE VIRAL ONCOPROTEIN TAX.

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HTLV-1 and HTLV-2 are complex retroviruses which share a similar genomic organization but differ in their pathobiology. HTLV-1, the first human retrovirus discovered, is the causal agent of an aggressive adult T-cell leukemia, whereas HTLV-2 is associated with a few cases of neurological disease. Both virus genomes encode an oncogenic protein, Tax, required for viral replication and capable to induce cell transformation. In addition, HTLV-1 and -2 generate an antisense transcript, named HBZ and APH-2, respectively, crucial for viral infection. Comparative studies between HTLV-1 regulatory proteins, Tax-1 and HBZ, and the HTLV-2 homologs, Tax-2 and APH-2, may highlight the contribution of viral proteins to oncogenesis.

The purpose of this study is to investigate the functional role of the viral regulatory proteins HBZ and APH-2 in the NF- $\kappa$ B cell signaling, which is constitutively activated by Tax in infected cells. We demonstrated that APH-2 and HBZ differ in their suppression of the NF- $\kappa$ B promoter activity. Unlike HBZ, the APH-2 protein is recruited by Tax in cytoplasmic structures and prevents the degradation of the inhibitor I $\kappa$ B, impairing p65 nuclear translocation. Furthermore, we found that APH-2, but not HBZ, forms complexes with the adaptor protein TRAF3, an upstream inhibitor of the alternative NF- $\kappa$ B pathway. We generated a TRAF3-KO cell line applying the CRISPR/Cas9 technique, which will allow us to investigate the HBZ and APH-2 role in modulating the alternative NF- $\kappa$ B cell signaling. This study may provide insight into the effect of host-viral interactions in human viral oncogenesis.