Investigating the Interplay Between HTLV-1 Viral Factors, Tax and HBZ, During T-cell Transformation

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Human T-cell leukemia virus-1 (HTLV-1) is a tumorigenic retrovirus that infects an estimated 15-20 million people worldwide. HTLV-1 is responsible for an aggressive T-cell malignancy termed adult T-cell leukemia (ATL). The incidence of disease associated with HTLV-1 infection is 2-6% over the lifetime of an infected individual, with symptoms taking up to 2-3 decades to present. Despite the long clinical latency period, HLTV-1-associated malignancies are chemotherapy resistant and the median survival time is <1 year. The detailed mechanism of how HTLV-1 transforms cells is still unknown, but several studies have indicated that two viral factors, Tax and HBZ, are individually linked to oncogenic transformation. However, the interplay between Tax and HBZ in the transformation process is unknown. Herein, we investigated the relationship between Tax and HBZ using a dual inducible lentiviral expression system in the IL-2-dependent murine T-cell line CTLL-2. Tax and HBZ cDNAs were cloned into the cumate-inducible and doxycycline-inducible expression vectors, respectively. These vectors were transduced into CTLL-2 cells and stable cellular clones were selected using drug resistance and single cell dilution. Clones that responded best to drug induction (as measured by mRNA levels and protein functionality) were selected for further experiments. Using the established CTLL-2 transformation assay, we sought to determine whether the presence of HBZ and Tax drives these cells from an IL-2-dependent to independent growth, a characteristic indicative of cellular transformation. Preliminary results suggest that both Tax and HBZ enhance transformation. Future experiments will determine the optimal dose of inducing drug and the level of viral proteins induced compared to established transformed cell lines, and the efficiency of IL-2-independent CTLL-2 growth following Tax and/or HBZ induction. Ultimately, our work will provide better insight into the transformation landscape of T-cells in humans and the molecular pathogenesis of ATL development.