

Dual cytoplasmic and nuclear localization of HTLV-1-encoded HBZ protein is a unique feature of Adult T cell Leukemia

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Background

Adult T-cell leukemia-lymphoma (ATL), is a highly malignant T-cell neoplasm caused by human T-cell leukemia virus type 1 (HTLV-1), characterized by a poor prognosis. Two viral proteins, Tax-1 and HBZ play important roles in the pathogenesis of ATL. While Tax-1 can be found in both of HTLV-1 asymptomatic carriers and patients with HAM/TSP chronic neurologic disease, HBZ is exclusively localized in the cytoplasm and only in the nucleus of ATL cell lines, suggesting that the nuclear localization of HBZ can be a hallmark of neoplastic transformation. To clarify this crucial point, here we investigated in detail the pattern of HBZ expression in ATL patients.

Methods

We made use of our monoclonal antibody 4D4-F3, that at present is a uniquely reported reagent, among the few described, able to detect endogenous HBZ by immunofluorescence and confocal microscopy in cells from asymptomatic carriers, HAM/TSP and ATL patients. Quantitative real time PCR was used to measure the relative abundance of spliced and unspliced HBZ mRNA isoforms in ATL patients.

Results

We found that HBZ localizes both in the cytoplasm and in the nucleus of cells of ATL patients irrespective of their clinical status, with a strong preference for the cytoplasmic localization. Tax-1 localized also in both compartments. ATL characterized by a prevalent cytoplasmic HBZ, similarly to HAM/TSP patients and AC carriers, mainly expressed the spliced HBZ isoform. Conversely, in ATL patients with a predominant HBZ nuclear localization, we observed a more abundant or similar unspliced vs spliced HBZ.

Conclusion

As HBZ is exclusively localized in the cytoplasm in asymptomatic carriers and in non-neoplastic pathologies, this finding shows that neoplastic transformation consequent to HTLV-1 infection is accompanied by the capacity of HBZ to translocate to the nucleus, which suggests a role of cytoplasmic-to-nuclear translocation in HTLV-1-mediated oncogenesis.

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