The Human T-cell Leukemia Virus type I basic leucine zipper factor upregulates the expression of the antioxidant Heme Oxygenase I

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Abstract

Adult T-cell leukemia/lymphoma (ATLL) is a relentless lymphoproliferative disease of CD4+ T-cells infected by the Human T-cell Leukemia Virus type I (HTLV-I), for which there are no effective treatments. Mounting evidence supports that the upregulation of antioxidants contributes to drug resistance and the development of the disease. Heme Oxygenase I (HMOX-I), which has been shown to enhance cancer cell survival upon exposure to stress-inducing agents, HMOX-I expression is regulated by the small Maf API proteins, which control transcription from promoter antioxidant response elements (AREs). A previous report, confirmed by our laboratory, shows that the HTLV-I antigen-encoded basic leucine zipper factor HBZ interacts with small Maf for recruitment to AREs in vitro. We questioned whether HBZ and small Maf regulate the expression of antioxidants like HMOX-I as a pro-survival strategy in ATLL cells. Our results show that HMOX-I is overexpressed in ATLL cells in a manner dependent upon both HBZ and the small Mafs. These proteins were found to be present at an ARE in the promoter of HMOX-I in vivo, and HBZ expression was observed to promote ARE transcription in a small Maf-dependent manner. HBZ is thought to be the major modulator of iron metabolism and functions to promote cell survival in ATLL cells, and recent evidence indicates that chronic iron overload and oxidative stress are hallmarks of ATLL. In this report we suggest that the expression of HMOX-I may be essential for promoting cell survival upon exposure to stress and that it could be a potential target for the treatment of ATLL.

HTLV-1 is the causative agent of Adult T-cell leukemia/Lymphoma

Leukemic HTLV-1+ CD4+ T-cells

Common sites of ATLL cell infiltration

HTLV-1 activates pro-survival mechanisms in ATLL cells to resist anti-cancer treatments

The viral oncoprotein HTLV-1 basic leucine zipper factor (HBZ) enhances the expression of some antioxidants

Elevated HMOX1 expression may correspond to ATLL disease progression

HMOX-1 is an essential iron-recycling enzyme

HMOX-1 promotes resistance to heme-induced oxidative stress in ATLL cells

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Hypothesis: HTLV-1-encoded, pro-angiogenic transcription regulators upregulate the expression of antioxidants to promote ATLL cell resistance to oxidative stress-induced cell death.

Conclusions and Future Directions

1. The antioxidant enzyme Heme Oxygenase I is overexpressed in some ATLL cell lines, as well as in a small group of ATLL patients.
2. HTLV-1 is present in bigger cell populations of ATLL.
3. HBZ promotes resistance to heme-induced oxidative stress in ATLL cells.
4. Will pharmacologic inhibition of HMOX-1 enhance sensitivity to anti-cancer drugs?