Is it NICE (nuclear import as a carcinogenic mechanism) to restrict HBZ in the cytoplasm?

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doi:10.3324/haematol.2021.278377

The paper by Forlani *et al.* found in this volume of Haematologica[1] presents an intriguing argument that the control over the subcellular localization of an antisense protein (HBZ, HTLV-1 basic-zipper factor) encoded by the human T-cell leukemia virus-1 (HTLV-1) critically controls its oncogenicity. HTLV-1 was the first human retrovirus identified[2] and is arguably the most carcinogenic agent know to humans.[3] Adult T-cell leukemia (ATL)[4] is a fatal CD4 type T-cell leukemia that occurs in 5% of HTLV-1 carriers. After 40 years of extensive research since the discovery of HTLV-1, the precise mechanism by which HTLV-1 transforms host T cells is not completely understood, and the prevailing paradigm points to two HTLV-1 factors, Tax-1 and HBZ[5] as the cause of T-cell leukemia. HBZ is a multi-functional protein and interacts with many cellular proteins. Not only that, HBZ transcripts have their own function as a cancer-promoting factor.[6] The group led by Roberto Accolla (last author of the paper) has been carefully studying the subcellular distribution of HBZ using a monoclonal antibody that they generated, and they observed that HBZ's localization differs in HTLV-1 infected cells in individuals manifesting different disease status. They found that HBZ exclusively localizes to the cytoplasm[7] in cells from asymptomatic carriers and patients with HAM/TSP (HTLV-1 associated myelopathy/tropical spastic paraparesis), a myelopathy that resembles multiple sclerosis in symptoms and the second major disease manifestation that HTLV-1 causes in humans. In contrast, they report in the current article that HBZ localizes in the nucleus in ATL cell lines. Though not exclusive, the nuclear localization of HBZ was distinct in *ex vivo* leukemic cells from ATL patients. They also showed that the nuclear localization of HBZ may be accompanied by a unidirectional displacement of HBZ from the cytoplasm to the nucleus. With these results, the authors suggest an attractive new hypothesis that the nuclear localization of HBZ is a hallmark of ATL and that the cytoplasmic-to-nuclear translocation of HBZ plays a major role in the leukemogenic mechanism of HTLV-1. These findings may help establish new diagnosis of ATL as well as providing new insights to the research on HTLV-1's oncogenesis. So, can a misguided subcellular localization of a particular protein lead to invoking an oncogenic capacity of the protein?

There are a few other examples that could shed light on this question.

Nucleophosmin (NPM) is an example. NPM shuttles between the nucleus and the cytoplasm and the cytoplasmic localization seems to facilitate its tumor promoting activities.[8] Another example is STAT3 (signal transducer and activator of transcription-3). STAT3 is a transcription factor involved in the signaling of many cytokines. Gain-of-function mutants of STAT3 are often found in many cancers including T-cell malignancies. Mutations of STAT3 that are associated with cancer cases cause a self-dimerization of this molecule, which enhances the nuclear transport and binding of STAT3 to the regulatory region of many target genes. In the case of STAT3, the control of subcellular localization *per se* is not directly connected to the oncogenicity of STAT3, but a mechanism that facilitates the nuclear translocation and DNA binding of STAT3 is likely making STAT3 an oncoprotein.

So how is the subcellular localization of HBZ controlled? It likely involves the interaction of HBZ with other proteins. Other groups have shown that HBZ can be retained in the cytoplasm by a T cell-specific molecule THEMIS,[9] but the Accolla group demonstrated that this does not explain the cytoplasmic distribution of HBZ in HAM/TSP patients.[10] Thus, an involvement of another protein for this observation is suggested. Hopefully, future studies will show the clue and help us know how HTLV-1 transforms host CD4 T cells and how we can control the fatal ATL which do not yet have curative treatment.

Disclosures

No clonflicts of interest to disclose.

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