a question about the role of ATF3 in ABC DLBCL. Interestingly, ATF3 has been shown before to contribute to the malignant growth of Hodgkin lymphoma cells and selective knockdown of ATF3 by RNA interference suppressed proliferation and decreased viability of Hodgkin cells.9 On the other hand, ATF3 overexpression resulted in increased apoptosis of solid tumors, as shown in PC3 human prostate cancer cells, HCT-116 human colorectal cancer cells, and others.10

Juilland and colleagues used short hairpin RNA–mediated silencing of signaling molecules, such as CARMA1, MALT1, MyD88, or IRAK1, results in depletion of ATF3 in cells of the ABC subtype.

AP-1 complexes of the c-Jun/ATF3 type promote survival of ABC DLBCL cell lines. Constitutive B-cell receptor signaling alone or in combination with activating mutations in Toll-like receptor signaling results in nuclear accumulation of c-Jun/ATF3 complexes. Short hairpin RNA–mediated silencing of signaling molecules, such as CARMA1, MALT1, MyD88, or IRAK1, results in depletion of ATF3 in cells of the ABC subtype.

This finding is an important contribution to our understanding of the signaling pathways used by lymphoma cells to survive.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Fujikawa et al described the epigenetic landscape in ATL using an integrative analysis of transcriptome and epigenome. They demonstrate that early after HTLV-1 infection, the viral transactivator of the X gene region, Tax, activates the transcription of key components of the polycomb-repressive complex 2, mainly the enhancer of zeste homolog 2 (EZH2), resulting in global alteration of trimethylation at histone H3 lys27 (H3K27me3) and epigenetic reprogramming involving more than half of cellular genes. These epigenetic changes could be reproduced through Tax transduction into normal T lymphocytes (see figure) whereas other viral proteins failed to do it, including the product of the HTLV-1 basic leucine zipper (HBZ) gene encoded by the antisense transcript. Importantly, the same profile is persistent in ATL even at late stages of the disease. Critically, this epigenetic-dependent global modification of host gene expression in ATL was reversible and was not due to EZH2 mutations found in other types of lymphoma, demonstrating that the ATL phenotype is Tax dependent.

It is well established that the HTLV-1 oncoprotein Tax initiates transformation in ATL. In addition to its effects on the viral promoter, Tax alters many cellular pathways: it activates transcription factors such as the nuclear factor-kB and the cAMP response element-binding protein (CREB), upregulates antia apoptotic proteins, represses the tumor suppressor p53, DNA polymerase β, proliferating cell nuclear antigen, and mitotic arrest deficient-1 checkpoint protein, and interferes with several cell cycle regulators and DNA repair. The current study by Fujikawa et al adds a new dimension in Tax oncogenic properties, namely the epigenetic-dependent global modification of host gene expression.

Through all of these activities, Tax acts as a powerful oncogene as demonstrated in transgenic mice models, whereby expression of Tax alone can induce ATL. However, that continuous Tax expression is required to sustain the malignant phenotype remains controversial. Indeed, Tax levels are very low in most ATL patients, making them undetectable by routine techniques. Furthermore, some ATL clones bear mutations in Tax predicted to abrogate its expression. This has suggested that, although Tax may have an initiating role in ATL, it could allow the accumulation of subsequent genetic changes that are the actual drivers of transformation. On the other hand, regulatory proteins that are expressed at very low levels, sensitivity of the detection method always remains an issue. For example, in Tax transgenic mice, Tax mRNA is present at very low levels, similar to acute ATL patients, and the protein remains undetectable in the transformed T cells. Furthermore, ATL-derived cells and HTLV-1–transformed cells are addicted to continuous Tax expression even when Tax protein is undetectable, providing a strong rationale for targeting Tax in ATL therapy. The recent demonstration of the efficacy of the Tax peptide-pulsed dendritic cell vaccine in treating ATL patients further strengthens this concept.

Despite significant progress in ATL therapy using the antiviral combination of zidovudine and interferon-α, most ATL patients continue to die rapidly from their disease, often in <12 months, stressing the need for novel effective targeted therapies. The current report by Fujikawa et al unravels that Tax fingerprint is almost everywhere in ATL through a powerful epigenetic-dependent global modification of host gene expression, either through upregulation or downregulation. These findings provide a strong rationale for directly targeting Tax in ATL therapy using arsenic trioxide and interferon α or anti-Tax vaccines as well as targeting this Tax global fingerprint on cellular genes using EZH2 inhibitors. Indeed, pharmacologic inhibition of EZH2 reversed the epigenetic disruption and selectively eliminated leukemic and HTLV-1–infected cells.

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Comment on Bernaudin et al, page 1814

Hydroxyurea for abnormal TCDs: safe to switch?

Patrick T. McGann
CINCINNATI CHILDREN’S HOSPITAL MEDICAL CENTER

In this issue of Blood, Bernaudin et al report that chronic red blood cell transfusions can be safely replaced with hydroxyurea therapy or bone marrow transplantation for a cohort of children with sickle cell anemia (SCA) and
Tax fingerprint in adult T-cell leukemia

Ali Bazarbachi