arm had a 100% reduction in annualized spontaneous bleeding and full resolution of target joints.

An interesting facet to this study was the flexibility given to the treating physician. Subjects in the prophylaxis group received 35 to 50 IU/kg weekly. The exact entry dose was determined by the treating physician. If there was no spontaneous bleeding in the first 26 weeks on this weekly dosing, dose and dosing interval could be adjusted to 75 IU/kg every 10 to 14 weeks. Importantly, the physician could increase or decrease the dose received based on clinical assessment. This flexibility gave the study a real-life feel, allowing physicians to make clinical judgments. Conceivably, this real-world design could ease the application in clinical use.

One of the vexing problems with all chronic illnesses is patient treatment fatigue. Decreasing dosing intervals may improve this issue in hemophilia B, increase adherence to prophylactic treatment, and prevent bleeding and associated joint arthropathy. Another key element of extended half-life rFIX products is the potential for higher trough levels which decrease the risk for breakthrough bleeding. A desirable trough level in the past has been considered to be >1% due to the notion that, by converting someone with severe disease to a phenotypic moderate hemophilia, spontaneous bleeding could be prevented. With the advent of these longer-acting FIX products, aiming for a higher trough level has become feasible and we have to ask whether 1% is enough for our patients with hemophilia. People with moderate and mild hemophilia (FIX levels of 2%-30%) still potentially experience microbleeding and certainly trauma/activity-related bleeding that can lead to undesirable outcomes. Combining increased compliancy with higher trough level allows for the normalization of activity and increasing long-term joint and overall health. The economic impact of this new paradigm certainly has to be considered. We are truly entering a new era for hemophilia B treatment.

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● ● ● LYMPHOID NEOPLASIA

Comment on Juilland et al, page 1780

ATF3, a new player in DLBCL cell survival

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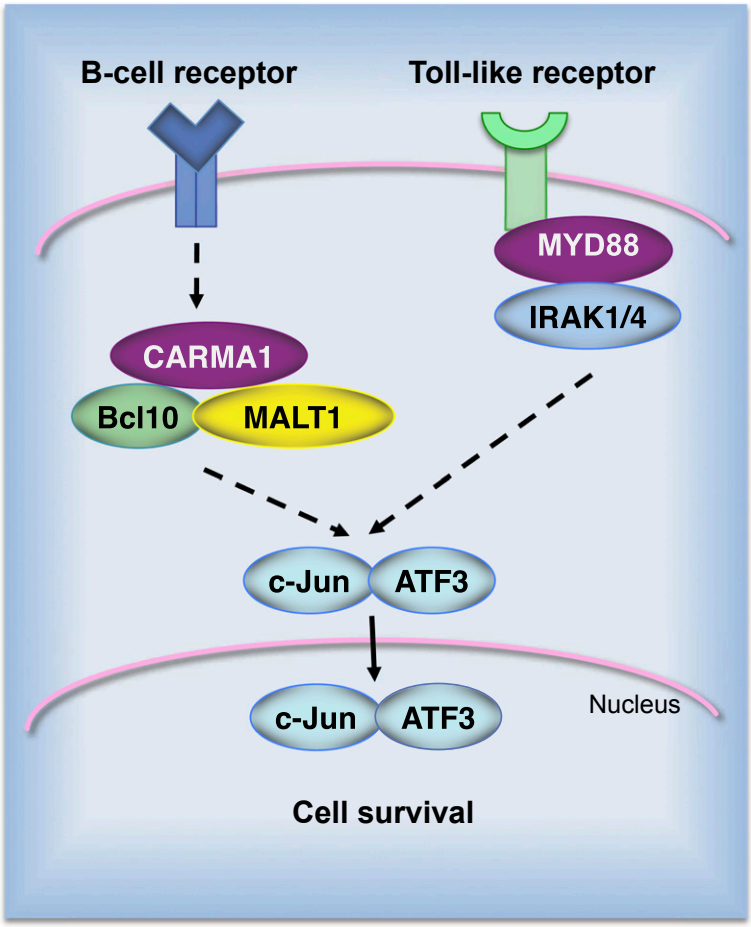
In this issue of *Blood*, Juilland and colleagues reveal the expression pattern and the role of different members of the activating transcription factor (ATF) family in survival of diffuse large B-cell lymphoma (DLBCL) cells.[1]

In adults, DLBCL is the most common lymphoid malignancy. It is a heterogeneous disease composed of multiple molecular subtypes that differ in their expression of hundreds of genes, their responsiveness to chemotherapy, and survival rates after chemotherapy.[2] The activated B-cell (ABC)–like subtype (ABC DLBCL) is the most aggressive form of DLBCL with the lowest cure rate. Initially, the constitutive activity of the nuclear factor–κB signaling pathway was identified as a major feature of ABC DLBCL.[3] However, recently, several independent studies have reported elevated expression levels and activity of Jun transcription factors in ABC DLBCL cell lines and clinical specimens.[4-6] Although Jun factors are primarily involved in regulating the cell cycle and apoptosis,[7] a large number of inducible genes contain Jun-binding sites in their promoters or enhancers and, therefore, they can be considered as Jun-target genes. But the complexity of this regulation starts with the fact that dimerization of Jun is required prior to its binding to DNA. Different Jun factors (c-Jun, JunB, and JunD) can form homodimers or heterodimers with proteins belonging to the FOS, ATF, and MEF families, creating the activator protein-1 (AP-1) transcription factor.[8] The composition of AP-1 complexes determines the genes that are regulated, either positively or negatively.

A report from Juilland and colleagues reveals novel and exciting findings regarding the role and molecular composition of AP-1 in DLBCL.[1] Using an unbiased biochemical approach, they identified ATF2, ATF3, and ATF7 as constitutive binding partners of Jun in lymphoma cells. Although Jun/ATF2 and Jun/ATF7 complexes were abundant in the majority of cell lines, ATF3 was exclusively expressed in cell lines derived from the ABC subtype of DLBCL (see figure). The clinical relevance of this observation was evaluated in patient biopsies. In a cohort of 350 DLBCL patients, the ATF3 messenger RNA level was significantly higher in the ABC vs the germinal center B-cell (GCB) subtype. Immunohistochemical analysis revealed strong nuclear ATF3 expression in tumors from ABC DLBCL patients. Altogether, these data raise



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.

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] Therefore, Juilland and colleagues used short hairpin RNA–mediated silencing of individual components of AP-1 complexes, as well as the dominant-negative construct that blocks AP-1 activity, to assess the role of Jun/ATF dimers in ABC DLBCL. They found that depletion of ATF3 reduced the viability of the majority of the ABC-type lymphoma cells but had no effect on GCB DLBCL. Interestingly, knockdown of ATF2 also affected cell survival but it simultaneously decreased the expression of ATF3. This effect is consistent with the fact that the transcription of the *atf3* gene is regulated by the c-Jun/ATF2 dimer. Thus, data presented in this study indicate that Jun/ATF complexes are important drivers of survival and proliferation of ABC DLBCL. This finding is an important contribution to our understanding the signaling pathways used by lymphoma cells to survive.

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

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● ● ● LYMPHOID NEOPLASIA

Comment on Fujikawa et al, page 1790

Tax fingerprint in adult T-cell leukemia

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In this issue of *Blood*, Fujikawa et al demonstrate that the human T-cell leukemia virus type 1 (HTLV-1) oncoprotein Tax induces an epigenetic-dependent global modification of host gene expression in adult T-cell leukemia-lymphoma (ATL). Hence, the fingerprint of Tax is all over ATL and this may be used for finally capturing ATL.[1]