EZH2. Thus, Van der Meulen and colleagues hypothesized that UTX-deficient cells might be more sensitive to inhibitors of these methyltransferases. Indeed, the authors found that UTX knockdown rendered leukemic cells more sensitive to DZNep, a small molecule whose cellular effects include inhibition of EZH2.

Intriguingly, although UTX and EZH2 have antagonistic methylation activity at H3K27, both UTX and EZH2 function as tumor suppressors in T-ALL.1,4-6 One potential explanation for this apparent discrepancy is that UTX and EZH2 may have distinct transcriptional targets. Indeed, additional H3K27 “writer” methyltransferases and “eraser” demethylases exist, so that UTX and EZH2 need not necessarily function as an antagonistic pair for the maintenance of balanced H3K27 methylation at individual loci. In fact, recent work has shown that JMJD3 (also known as KDM6B), a UTX-related H3K27 demethylase, is bound by NOTCH1 and required for the maintenance of NOTCH1-induced T-ALL.4 By contrast, UTX does not bind NOTCH1 and suppresses NOTCH1-induced tumorigenesis.4 Thus, a speculative model to explain these observations is that EZH2 and JMJD3 may function as an antagonistic “writer-eraser” pair, with the UTX “eraser” being antagonistic to a different H3K27 methyltransferase. Such a model would mimic the antagonistic relationships that are conserved across substrates for some kinase-phosphatase pairs.7

The tumor suppressor function of UTX could also be mediated by functions independent of its ability to demethylate H3K27. Such possibilities include demethylation of lysine residues on nonhistone substrates or demethylase-independent functions. For example, UTX has been shown to interact with the switch/sucrose nonfermentable (SWI/SNF) chromatin-remodeling complex,8 a key tumor suppressor in diverse human cancers. Indeed, recent data have demonstrated that the tumor suppressor BCL11B, which is recurrently inactivated in human T-ALL, is a dedicated SWI/SNF subunit.9,10 Thus, UTX deficiency might represent an alternative mechanism for disabling the tumor suppressor function of SWI/SNF in T-ALL.

Unraveling the role of chromatin-modifying enzymes in T-ALL has important potential therapeutic implications. The overexpression of oncogenic transcription factors plays key roles in T-ALL, yet transcription factors have proven to be largely intractable targets for drug development. However, transformation by oncogenic transcription factors is strongly influenced by the accessibility of their binding sites within DNA, which is highly regulated by chromatin-modifying enzymes such as UTX and EZH2. These enzymes are much more tractable therapeutic targets than transcription factors. Thus, unraveling the precise role of such chromatin-modifying enzymes in T-ALL pathobiology could reveal therapeutic strategies to specifically reverse oncogene expression programs. Indeed, the work of Van der Meulen et al1 and of Ntzniachristos et al4 provides a compelling rationale for testing inhibitors of 2 such enzymes, EZH2 and JMJD3, in molecularly defined subsets of T-ALL.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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hematopoietic stem cell transplantation (AlloSCT), which is only applicable in a minority of patients, the clinical benefit of these systemic treatments should be carefully balanced against their toxicity and side effects. However, the decision of whether systemic chemotherapy or one of these nonchemotherapeutic systemic agents should be used in these patients is difficult to make, because comparative studies have not been done. The study by Hughes et al fills this gap by comparing retrospectively the efficacy of many chemotherapeutic and nonchemotherapeutic systemic agents in a group of 198 patients with MF and SS.

A particular strength of the study is the selection of time to next treatment (TTNT) as the primary end point. In current trials, the extent of skin disease is evaluated using detailed scoring systems such as the modified severity-weighted assessment tool (mSWAT). However, the measurement tool was only recently adopted and its use is limited in a retrospective study. The TTNT used by the authors provides genuine insight into the durability of responses as assessed in daily practice, and it provides a clinically relevant measure of effectiveness.

Previous studies showed that aggressive systemic chemotherapy in the early stages of MF is associated with considerable morbidity but does not result in increased survival. In the present study, it was found that in patients with only patches and plaques (stages IA–IIb), and also in patients with only skin tumors but no extracutaneous disease (stage IIB), α-interferon gave significantly longer TTNT than HDAG and chemotherapy. In addition, in patients with advanced stages of disease with lymph node and blood involvement (stages IVa–IVb), treatment with α-interferon and HDAG resulted in longer TTNT than did systemic chemotherapy. Also when stratified by skin (T) score, α-interferon provided significantly better disease control than chemotherapy for T1 (patches and plaques <10% body surface area), T2 (patches and plaques >10% body surface area), and T4 (erythrodermic disease). Finally, extracorporeal photopheresis was especially effective in erythrodermic (T4) patients.

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***CLINICAL TRIALS & OBSERVATIONS***

Comment on Kolstad et al, page 82

**Dendritic cells and lymphoma cells: come together right now**

**Nina Bhardwaj and Joshua D. Brody Icahn School of Medicine at Mount Sinai**

In this issue of Blood, Kolstad et al report an elegantly designed and well-implemented study showing that intratumoral injection of ex vivo-produced immature dendritic cells (DCs), granulocyte macrophage colony-stimulating...