levels facilitate BCR signaling, which is advantageous to the cells, we might expect selection for this state. Indeed, Mraz et al find that miR-150 levels negatively correlate with disease progression (Rai stage). As for regulation, the authors provide a hint that miR-150 might be controlled epigenetically.

Finally, an exciting new field is the development of miR-based therapeutics that either downregulate the function of oncogenic miRs or upregulate the expression of tumor-suppressive miRs, such as the liposome-based miR-3-34 mimic currently in phase 1 trials (reviewed in Ling et al). Because Mraz et al identified miR-150 as a potential key regulator of PI3K and because it has been showed in follicular B cells that miR-185 regulates the expression of Bruton tyrosine kinase, it does not take a lot of imagination to speculate on the development of miR mimetics to target key signaling cascades in CLL.

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

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the presence of a proline residue, in addition to the cysteine, as in the original mutant, resulted in signaling (see figure). This could explain why no simple cysteine substitutions or insertions have been reported as yet.

The TSLP receptor is a different story. It shares the IL-7Rα chain, but uses CRLF2 as a second chain rather than γc. Unlike the insertions in IL-7Rα in T-ALL, overexpression of CRLF2 in B-cell-derived acute lymphoblastic leukemia (B-ALL) is a frequent pattern that is created by chromosomal rearrangements.7-10

Overexpression confers a modest ligand-independent signal in vitro and may require TSLP in vivo to mediate its leukemic effects. CRLF2 can also display a gain-of-function mutation, F232C, that gives a stronger ligand-independent signal and is found in a subset of CRLF2 overexpressors in B-ALL. In the current report,1 a noncysteine mechanism is analyzed in mutations of CRLF2 in B-ALL. The study examined one such CRLF2 mutant, which, like the atypical IL-7Rα mutants, occurred within the transmembrane region and, in BaF3 cells induced homodimerization. This CRLF2 mutant required coexpression of IL-7Rα to signal and grow as leukemia in mice, suggesting it may also heterodimerize with IL-7Rα in an orientation that activates their associated Janus kinases.

These studies point to new leukemogenic signaling mechanisms and reinforce the IL-7/TSLP axis as therapeutic targets in ALL.

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Comment on Placke et al, page 13

CDK6, a new target in MLL-driven leukemia

Iléana Antony-Debré and Ulrich Steidl ALBERT EINSTEIN COLLEGE OF MEDICINE

In this issue of Blood, Placke et al identify the cell-cycle regulator CDK6 as a promising new target in mixed lineage leukemia (MLL)-rearranged acute myeloid leukemia (AML) and show that its downregulation or pharmacological inhibition leads to growth inhibition and differentiation of MLL-driven leukemic cells.1

Chromosomal rearrangements involving the MLL gene, located on chromosome 11q23, are found in 5% to 10% of pediatric and adult AML and are usually associated with a poor prognosis. More than 50 fusion partners have been described, with frequent
IL-7 and TSLP receptors: twisted sisters

Scott K. Durum