malignancy (see figure). In addition to miR-21, other implicated miRNAs include mir-181ab1, which appears to dampen the expression of negative regulators of Notch such as *Nrarp*, thereby helping Notch clear the signaling threshold that is required for leukemogenesis; miR-451, a Dicer1-independent miRNA that is repressed by Notch, an alteration that contributes to Notch's ability to upregulate and sustain *Myc* expression[6]; miR-193b-3p, which suppresses Notch-induced T-ALL development by repressing *Myb*,[7] a "pioneer" transcription factor that dysregulates other oncogenes that contribute to T-ALL development; and numerous other "onco-miRNAs" targeting a who's who of tumor suppressors in T-ALL, including *Ikzf1*, *Pten*, *Phf6*, *Bim*, *Nf1*, and *Fbxw7*,[8] in addition to the aforementioned *Pcdc4*.[1] This panoply of miRNAs may prove to be the tip of the proverbial noncoding RNA iceberg, as other recent papers have implicated long intervening noncoding RNAs, including some that are directly regulated by Notch,[9,10] as participants in T-ALL pathogenesis.

The challenge now is to translate these insights into new approaches that inform the diagnosis and improve the treatment of T-ALL and other blood cancers. An increasing number of diagnostic tests are coming on line that are centered on detection of specific miRNAs in situ, in tumor cell lysates, and free in blood. Therapeutic miRNA targeting strategies also are in various stages of development, including agents that specifically target miR-21 or that are preferentially active in the tumor microenvironment. Much additional work is needed to determine if these (or any of the many other leads being pursued) can be brought to fruition, to the benefit of patients with T-ALL and other blood cancers.

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

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● ● ● **LYMPHOID NEOPLASIA**

New mutation in hairy cell leukemia


Tadeusz Robak and Piotr Smolewski   MEDICAL UNIVERSITY OF LODZ

In this issue of *Blood*, Dietrich et al make the first observation of the presence of deleterious *CDKN1B* mutation in 16% of patients with hairy cell leukemia (HCL).[1] Furthermore, in the majority of patients, the *CDKN1B* mutation was clonal, suggesting that this mutation plays a role in the pathogenesis of HCL.

HCL is a rare subtype of B-cell chronic lymphoid leukemia, characterized by progressive pancytopenia, splenomegaly, and infiltrations of the bone marrow, liver, and spleen, with B lymphocytes possessing cytoplasmic projections that appear as fine hair-like microvilli. Over the last 5 years, significant progress has been made in the understanding of the molecular biology of this disease. In particular, the discovery of the *BRAF*V600E mutation provided a breakthrough in our understanding of
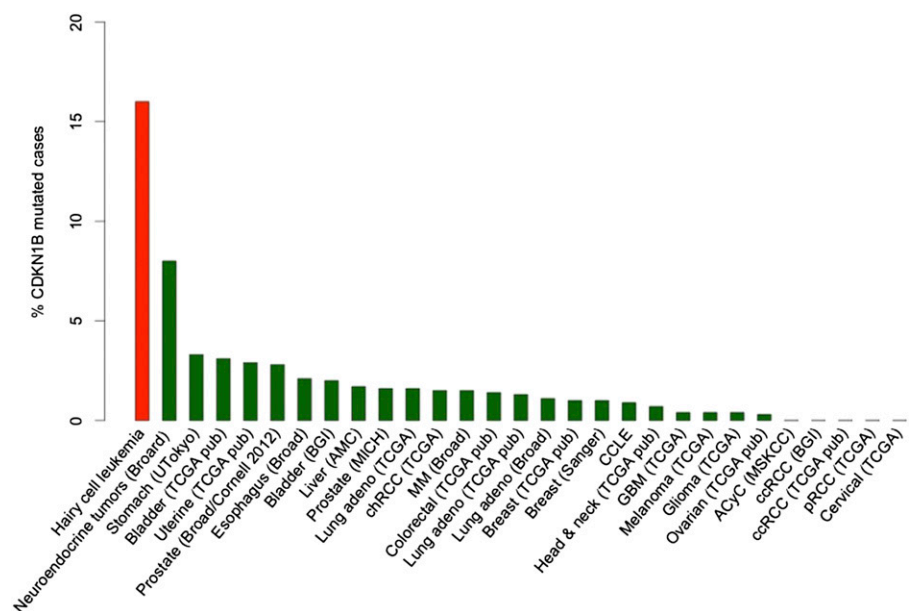
Frequency of *CDKN1B* mutations across different cancer entities. The highest frequency of *CDKN1B* mutation is observed in HCL. See Figure 1C in the article by Dietrich et al that begins on page 1005.

the pathogenesis of HCL.[2] Although the BRAFV600E mutation is clonally presented in almost 100% of classical HCL patients, it has been not identified in patients with other B-cell malignancies. In addition, 2 novel mutations in exon 11 of the BRAF gene were detected in BRAFV600E-negative cases of HCL. This understanding of the BRAFV600E mutation has provided a rationale for the diagnosis of HCL, with potential therapeutic implications.[3,4] However, the BRAFV600E mutation is not detected in the HCL variant (HCL-v) and IGHV4-34 variants of HCL.[5] Recently, vemurafenib, an ATP-competitive BRAF inhibitor, has been shown to have potent antitumor activity in BRAFV600E-mutated HCL patients.[6]

Thus far, no other recurrently mutated genes coexisting with BRAFV600E mutations have been identified in patients with classical HCL. Dietrich et al report their results of whole-exome sequencing and targeted sequencing analysis in 3 HCL patients refractory to purine analog, who received vemurafenib. This part of the study was followed by testing of novel mutations in a larger cohort of 81 patients with classical BRAFV600E-mutated HCL, who were refractory to purine analog.[1] The authors identify mutations in EZH2 and ARID1A and recurrent inactivating mutations of the cell cycle inhibitor CDKN1B, in addition to mutations in BRAFV600E. Until this study, CDKN1B mutations had never been investigated specifically in HCL. Deleterious CDKN1B mutations were identified in 13 of 81 (16%) analyzed patients by deep sequencing of CDKN1B. In addition, in 11 of those 13 patients, the CDKN1B mutation was clonal, implying a role of this mutation in the pathogenesis of HCL. The authors report that mutation in CDKN1B is the second most common mutation in HCL.

The CDKN1B gene encodes the cyclin-dependent kinase inhibitory protein p27, which belongs to the Cip/Kip class of cyclin-dependent kinase inhibitors and inactivates the cyclin E-CDK2 complex. This protein performs complex functions in cell cycle regulation and is a known tumor suppressor.[7] The p27 protein can exert either stimulatory or inhibitory effects on cell proliferation, cell motility, or apoptosis. Moreover, the upregulation of p27 can participate in the resistance of tumor cells to anticancer treatment.[7] At high levels, p27 binds to the cyclin E-CDK2 complex, inhibiting its activity and allowing cell cycle arrest. In contrast, lower levels of p27 protein stabilize cyclin D-CDK4/6 complexes and facilitate cell cycle progression.

Recent studies have shown that the CDKN1B gene may also play a role in the pathogenesis of other hematologic malignancies, including T-cell prolymphocytic leukemia (T-PLL), acute myeloid leukemia (AML), and lymphomas.[8,9] An important role in the pathogenesis of T-PLL is played by CDKN1B haploinsufficiency.[8] AML patients with low CDKN1B expression were found to demonstrate longer event-free survival than those with intermediate or high expression.[9] In chronic lymphocytic leukemia, high levels of p27 are associated with rapid disease progression and poor outcome.[10] However, CDKN1B mutations are very rare in these leukemias and other malignancies and do not coexist with BRAFV600E (see figure). Future studies should clarify whether the mutation of CDKN1B may contribute to the pathogenesis of HCL and what its impact on clinical outcome could be. In the highlighted study here, the CDKN1B mutation was found to have no impact on clinical characteristics or response to standard therapy with purine analog. However, further analysis of the signaling pathways related to this mutation may allow a clearer understanding of this finding and its possible application in clinical practice, both as a prognostic factor and a specific therapeutic target.

In conclusion, Dietrich et al demonstrate that CDKN1B is inactivated in 16% of patients with classical HCL and that it is the second most commonly mutated gene in HCL. These observations strongly suggest that CDKN1B plays a potential role in the biology and pathogenesis of HCL, particularly in neoplastic cell cycle deregulation and tumor suppression.

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● ● ● **MYELOID NEOPLASIA** ▬▬▬▬▬▬

Cladribine for mastocytosis: benefits and risks

Cem Akin HARVARD MEDICAL SCHOOL

In this issue of *Blood*, Barete et al report the safety and efficacy of cladribine in 68 adult patients with mastocytosis.[1] Cladribine (2–chlorodeoxyadenosine) is a purine analog that causes apoptosis in cells after phosphorylation intracellularly