**LYMPHOID NEOPLASIA**

Comment on Clifford et al, page 1021

**SAMHD1: a new gene for CLL**

Davide Rossi1

In this issue of Blood, Clifford et al broaden the horizons of chronic lymphocytic leukemia (CLL) genetics by adding **SAMHD1** to the compendium of driver genes recurrently mutated in this tumor.1,2

**SAMHD1** encodes the sterile α motif and histidine-aspartic domain (HD) containing protein 1, a deoxynucleoside triphosphate triphosphohydrolase that degrades the intracellular pool of deoxynucleoside triphosphates (dNTPs) into their deoxynucleosides and inorganic triphosphates (see figure).3,4 The final consequence of SAMHD1 activity is the depletion of the cellular pool of dNTPs, which are required for DNA polymerase functioning and, ultimately, for DNA synthesis (see figure).3

Before being identified as a cancer gene by Clifford et al, **SAMHD1** was already known in hereditary genetics because it was constitutively mutated in Aicardi-Goutières syndrome, an inherited autoimmune inflammatory encephalopathy.6 Clifford et al initially pointed to **SAMHD1** as a potential CLL gene after their pivotal clinical observation of early-onset CLL in a young adult subject affected by Aicardi-Goutières syndrome. By genome sequencing, CLL cells of this patient were devoid of somatic genetic lesions that are well-known drivers of this leukemia, thus supporting the notion that the germ-line homozygous mutation of **SAMHD1** in this patient was sufficient to cause CLL. In parallel, the same authors and others have shown that somatically acquired **SAMHD1** mutations also exist in CLL as founder genetic events.7,8

Based on these observations, Clifford et al propose that **SAMHD1** mutations could play an oncogenic role in the early pathogenesis of CLL and provide several lines of experimental evidence in support of this hypothesis. First, **SAMHD1** is recurrently affected in 3% to 11% of CLL, depending on the case mix of the series investigated, with a prevalence that is in the range of that of well-established driver genes in this leukemia. Second, **SAMHD1** mutations are generally represented in the entire CLL clone, indicating that they are early events in CLL clonal evolution. Third, **SAMHD1** mutations include disrupting events and often couple with loss or acquired uniparental disomy of the second allele. This molecular pattern recapitulates a typical double hit mechanism of tumor suppressor gene inactivation selected to disrupt **SAMHD1**. Consistently, **SAMHD1** molecular lesions associate with markedly reduced mRNA and protein expression in CLL cells. Fourth, a fraction of **SAMHD1** mutations is common to both CLL and Aicardi-Goutières syndrome, where these variants have well-established functional consequences.9,10 Finally, **SAMHD1** is involved in the response to DNA damage and in restraining cell survival and proliferation, with the latter cellular process being favored by the mutant form of **SAMHD1**.

Overall, these results point to a tumor suppressor role of **SAMHD1** in CLL. However, several biological questions remain to be elucidated. Do **SAMHD1** mutations affect the biochemistry of the protein and its function as deoxynucleoside triphosphate triphosphohydrolase? Which are the specific mechanisms mediating the antiproliferative and proapoptotic effects of **SAMHD1** and how are these mechanisms turned off by mutations? What is the role of **SAMHD1** in normal B-cell homeostasis? Does **SAMHD1** conditional deletion promote in vivo B-cell tumor development?

The study by Clifford et al also opens new questions in the field of CLL predisposition. Much epidemiologic evidence is in support of the genetic susceptibility of CLL, and genome-wide association studies have allowed the identification of several previously unexpected CLL risk loci and genes.9 The discovery by Clifford et al of a **SAMHD1** germ-line mutation as a CLL driver points to **SAMHD1** and its polymorphisms as attractive candidates to be further explored in the search of risk alleles for CLL.

From a clinical standpoint, Clifford et al propose **SAMHD1** mutations as a potential biomarker of chemoresistance in CLL. This is supported by the clinical observation of poorer responses to first line immunochemo therapy among **SAMHD1**-mutated CLL patients and by the biological observation that loss of **SAMHD1** enhances resistance to chemotherapy-induced DNA damage.1 However, larger and
well-designed clinical studies and preclinical models are required to validate SAMHD1 mutations as predictors of treatment refractoriness in CLL and to dissect the biology of chemoresistance associated with these mutations. An intriguing mechanism might link SAMHD1 defects to chemoresistance. The cytotoxicity of fludarabine, a cornerstone of current CLL treatment, depends on the rate of its incorporation into tumor DNA in place of dNTPs. Because dNTPs compete with fludarabine for incorporation into DNA, their excess in tumor cells confers resistance to these agents.13 SAMHD1 acts as a negative regulator of the intracellular dNTP pool, and therefore, its defects in CLL cells may cause resistance to fludarabine by favoring the accumulation of cellular dNTPs.

As witnessed by the authors, they are at the beginning of a new story in CLL biology.

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REFERENCES
5. Sze A, Olagnier D, Lin R, van Grevenynghe J, Hiscott J. SAMHD1 host restriction factor-1/SDF-1) secreted by stromal cells, attracting and homing into the lymph node/lymph nodes and bone marrow is an essential part of the disease pathogenesis and progression. CLL dissemination inside tissue microenvironments is actively coordinated by crosstalk between leukemic cells and stroma. Attraction of CLL cells is mediated by gradients of chemokines through activation of corresponding chemokine receptors. In the marrow, CXCL12 CXCR4 signaling, thus removing CLL cells from spontaneous and drug-induced apoptosis.

In this issue of Blood, Hoellenriegel et al provide evidence that NOX-A12, an RNA oligonucleotide able to bind and neutralize CXCL12, effectively interferes with chronic lymphocytic leukemia (CLL) cell chemotaxis and stroma-mediated drug-resistance.1

Lympocytes continually recirculate from blood to tissues and back to the bloodstream again. Trafficking is mediated by transient interactions with endothelium through adhesion molecules and chemokines that trigger integrin activation, thus inducing firm adhesion and transendothelial migration into tissues where stromal cells guide lymphocyte homing and retention.2

In CLL, trafficking and homing into the lymph nodes and bone marrow is an essential part of the disease pathogenesis and progression. CLL dissemination inside tissue microenvironments is actively coordinated by crosstalk between leukemic cells and stroma. Attraction of CLL cells is mediated by gradients of chemokines through activation of corresponding chemokine receptors. In the marrow, CXCL12 CXCR4 signaling, thus removing CLL cells from spontaneous and drug-induced apoptosis.1

The necessity of CLL cells to localize into tissues and to establish an interactive network of cellular contacts with microenvironmental elements of immune and stromal systems may represent the Achilles heel of leukemic cells. How can we interfere with CXCL12/ CXCR4 signaling, thus removing CLL cells from the nurturing and protective microenvironment and making them more vulnerable to conventional therapy? Different strategies have been developed to inhibit this supporting signal, mainly focusing on the
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