To the editor:

Integrity of the CBL gene in mature B-cell malignancies

Identification of biomarkers for response to novel therapeutic agents is an essential step for the success of tailored treatments in cancer. Preliminary data from clinical trials indicate that inhibitors of the spleen tyrosine kinase (SYK) may be efficacious in subsets of diffuse large B-cell lymphomas (DLBCL) and chronic lymphocytic leukemias (CLL).1

SYK is a component of the signaling cascade initiated by engagement of the B-cell receptor (BCR) and a key element in the transduction and amplification of these responses. SYK activity is induced by its binding to the immunoreceptor tyrosine-based activation motifs (ITAM) of the BCR, by SRC family kinases, and by autophosphorylation.2 In turn, SYK expression and activity is abrogated by the E3 ubiquitin ligase activity of the Casitas B-lineage lymphoma (CBL) protein, a central negative regulator of multiple tyrosine kinases in hematopoietic lineages.3,4

Recent in vitro observations suggested that elevated SYK activity could predict response to SYK inhibitors in DLBCL and CLL.5,6 However, it is unclear whether the high SYK activity found in these tumors relates to an innate program of the cancer cell’s normal counterpart, or to a well-defined pathogenetic event. Concerning the latter, loss of CBL activity is a prime candidate because mouse models with B-cell–specific ablation of both Cbl and Cbl-b (Cbl+/− Cblb−/−) display enhanced Syk phosphorylation.6 Furthermore, several recent reports showed that somatic CBL mutations in the critical linker and ring finger domains (exons 8 and 9) are frequent in myeloid malignancies, particularly (but not exclusively) in myelodysplasia/myeloproliferative neoplasms (MDS/MPN) with acquired uniparental disomy (aUPD) at chromosome 11q.7,8 These recent findings, together with the prominent negative regulatory role of CBL toward SYK and the elevated SYK activity in subsets of mature B-cell malignancies, prompted us to investigate the integrity of the CBL gene in a large collection of mature lymphoid tumors.

We directly sequenced the polymerase chain reaction (PCR) products of exons 8 and 9 of the CBL gene in 203 tumors, including 92 DLBCLs (72 primary lymphomas and 20 cell lines), 79 CLLs, 15 mantle cell lymphomas, 9 multiple myelomas and 8 T-cell lymphomas, obtained according to the guidelines of the institutional review board of the University of Texas Health Science Center at San Antonio. The clinical and molecular characterization of this tumor collection has been reported previously.11,12 Our strategy involved using PCR primers localized to intronic regions of exons 8 and 9 of the CBL gene (described in Grand et al11), thus also allowing for the detection of disrupted splice sites, which were previously associated with aberrant exon 8 splicing in acute myeloid leukemias.7,9 Automated sequencing of the PCR products was performed at Agencourt Bioscience Corporation, and the sequence traces analyzed with Mutation Surveyor, Version 2.6 (SoftGenetics).

No pathogenetic nucleotide changes were identified in the CBL gene in any of the mature lymphoid malignancies analyzed. Considering the number of cases investigated, and the reported frequency of CBL mutations in unselected or selected myeloid malignancies (~1% to ~33%),7,9 we conclude that CBL mutations are not a prominent feature of mature B-cell malignancies. These data agree with recent evidence showing that aUPD at 11q is rare in B-cell lymphomas,17 and indicate that the molecular mechanism for the elevated SYK activity found in subsets of DLBCL and CLL remains to be defined.
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References


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