become unable to proliferate and differentiate into plasma cells as a result of chronic receptor stimulation by low-affinity self-antigens.8 Anergic B cells in mice demonstrate activated signal transduction, particularly via the Erk1,2 and NFAT1 pathways. Normally, antigen-specific B-cell receptor engagement causes activation of PI3 kinase with downstream activation of the Akt survival pathway and cell proliferation. Anergic B cells also have limited life spans and readily undergo apoptosis unless they are constantly challenged with self-antigen. Chronic self-antigen stimulation, then, could be responsible for maintaining viability of CLL leukemia in a subset of patients.

Currently, the use of an anergic molecular signature to define CLL patient subsets may not be relevant to clinical management of their disease, as the Akt versus Erk1,2 signaling subsets apparently do not account for prognostic differences as do IgVh mutational signatures. Approximately half of patients with phosphorylated Erk1,2 and half of those with phosphorylated Akt are defined by Muzio et al as having mutated IgVh (see figure). The other half have unmutated IgVh signatures. The authors further report that these molecular signatures of anergy also do not correlate with expression of either CD38 or ZAP70. The main take-home message implicit in these findings and in the investigation of signal transduction pathways is that potential targeted therapy for a given patient should be chosen depending upon defining the nature of the specific pathways activated in their leukemic cells.

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Ligandless receptors find a role

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In this issue of Blood, Li and colleagues propose a better surrogate for IGHV mutations in CLL.

The discovery that patients with chronic lymphocytic leukemia (CLL) who showed somatic hypermutation of their immunoglobulin heavy chain variable region genes (IGHV) lived on average 3 times longer than those who did not,1,2 revolutionized the study of CLL and has greatly influenced the design and understanding of clinical trials. Assaying for such mutations seems complicated, and the prospect is sufficiently intimidating to deter most routine laborato-

ries from offering the test. Instead, there has been a search for a surrogate marker, especially one that can be assayed by a familiar technique such as flow cytometry.

Originally, the expression of CD38 looked promising,1 but that was shown to be discordant with IGHV mutations in up to 30% of cases—so much so that it could be regarded as an independent prognostic factor. Moreover, it could change during the course of the disease.3 Gene-expression pro-

filing of the 2 subtypes of CLL suggested that the Syk family tyrosine kinase gene ZAP-70 was the best discriminator between them,4 but translating this finding into a flow cytometry test has proven troublesome, and none of the many possible assays has gained universal acceptance. One commonly used assay shows only 77% concordance with IGHV mutations.5

The immunoglobulin superfamily is a large group of cell-surface and soluble proteins that share structural features with immunoglobulin molecules, and includes receptors, coreceptors, and costimulatory molecules. The well-known receptors for the Fc portion of immunoglobulin are members of this family. Recently, a large family of Fc receptor–like molecules (FCRLs) with preferential expression on B lymphocytes has been discovered.6 Genes coding for them localize to chromosome 1q21. There is no convincing evidence that they bind immunoglobulin, and so far, they lack ligands. In this issue of Blood, Li and colleagues have demonstrated that some of the FCRLs are expressed more densely on CLL cells from patients with mutated IGHV genes than on those from patients with unmutated IGHV genes. A flow cytometric assay using a monoclonal antibody against FCRL2 and measuring mean fluorescence intensity (MFI) discriminated between CLL cells with mutated and unmutated IGHV genes with a concordance of 94.4%. Among 107 patients with CLL, median time to first treatment was more than 4 times as long for patients whose cells expressed FCRL2 with an MFI ratio of 4.2 or greater. FCRL2 seems to be stably expressed over time.

Should measurement of FCRL2 expression replace IGHV mutations as a prognostic marker? We must first see confirmation of these results in a rather larger series of patients, but given that DNA sequencing is cheaply available from commercial sources and that matching the sequence to the database is performed by a computer program, one wonders why so few laboratories have established the assay for IGHV mutations. In any event, discordances between the various prognostic markers and the clinical picture promise to give us a clearer insight into why some cases of CLL progress and some do not.

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The immune synapse (IS) forms in response to antigen presentation and T-cell receptor engagement. Following stimulation, components critical for transmitting the activation signal downstream assemble and orchestrate the events required for proper T-cell response. One key step in this process involves reorganization of the actin cytoskeleton and formation of actin-rich signaling complexes. This process requires WAVE2 and HS1, among other molecules; defects in these proteins impair the response. Thus, understanding the way in which these molecules are regulated will illuminate the way T-cell responses are generated.

The knowledge that tyrosine phosphorylation of HS1 is required for its ability to promote actin polymerization at the IS, and that c-Abl kinase activity is important for IL-2 production, an important consequence of T-cell activation, led Huang and colleagues to explore the link between c-Abl and formation of the IS. c-Abl, the tightly regulated protein tyrosine kinase that is aberrantly expressed as a Bcr fusion in chronic myelogenous leukemia (CML), has been implicated in a wide range of cellular functions. Unlike its oncogenic Bcr/Abl counterpart, c-Abl shuttles between the cytoplasm and the nucleus and influences proliferation, survival, the DNA damage response, and other processes. However, despite the long-standing observation that the immune response is impaired in c-abl-null mice, a clear understanding of the mechanisms underlying this impairment has been slow to emerge.

By using imatinib, a drug that inhibits c-Abl activity and shRNA, the authors demonstrate that c-Abl interacts with HS1 and that c-Abl kinase activity enhances HS1 phosphorylation and proper formation of the IS. Interestingly, HS1 phosphorylation by ZAP-70, another regulatory molecule that affects IS formation, is not affected by c-Abl, highlighting the importance of multiple phosphorylation steps in achieving proper regulation. Using video microscopy, the authors reveal that c-Abl affects the IS in a second way. Unlike HS1-deficient cells, which fail to participate in IS formation, whether c-Abl exerts its effect through direct interaction or through interaction with another component of the WAVE complex requires additional work. c-Abl deficiency also affects chemokine-induced T-cell migration, and discovering whether this phenomenon reflects effects on HS1 or WAVE2 or other molecules should provide a clearer understanding of the mechanisms involved in chemotaxis. Lastly, and perhaps most intriguingly, this work raises the possibility that complications with infection seen in imatinib-treated CML patients stem from inhibition of c-Abl and an impaired T-cell response.

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MM-induced osteolysis: partners in crime

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In this issue of Blood, Qiang and colleagues explore in detail the role of Wnt inhibition in the progression of multiple myeloma–induced OBLs.
Ligandless receptors find a role

Terry J. Hamblin