become unable to proliferate and differentiate into plasma cells as a result of chronic receptor stimulation by low-affinity self-antigens.\textsuperscript{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 Muzzio 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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Comment on Li et al, page 179

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\textsuperscript{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-
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COMMENT ON HUANG ET AL, PAGE 111

EnABling the immune synapse

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In this issue of Blood, Huang and colleagues reveal new insights into the mechanism by which c-Abl protein regulates T-cell responses through actin-mediated effects on the immune synapse.

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.1 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,2,3 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, in which actin-rich structures disassemble quickly, c-Abl-deficient cells were compromised in spreading and formation of lamellipodia. These defects appear to involve effects on WAVE2, which fails to localize correctly when c-Abl activity and expression are suppressed.

In addition to making important contributions to our understanding of the regulation of IS formation, these experiments raise a number of intriguing questions. For example, do independent signals trigger phosphorylation of HS1 by ZAP-70 as opposed to c-Abl? Perhaps ZAP-70–mediated phosphorylation of HS1 allows the c-Abl SH2 domain to bind to HS1, thereby facilitating c-Abl–mediated phosphorylation of another residue on HS1, allowing the molecule to fully participate in IS formation. Although WAVE2 is crucial for actin polymerization and IS formation, whether c-Abl exerts its effects 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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COMMENT ON QIANG ET AL, PAGE 196

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