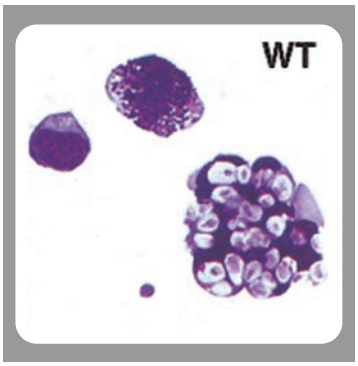
mechanisms of mast cell secretion in response to crosslinking immunoglobulin E (IgE) receptors and secretagogues have been studied extensively, not much is known about how bacteria and bacterial products activate secretion of the mast cell mediators of host defense. Now, in this issue of *Blood*, Edelson and colleagues (page 2214) have shown that mast cell expression of the integrin α2β1, a receptor for extracellular matrix collagens and for at least one cell-surface molecule, E-cadherin, is required for PMN influx and interleukin-6 (IL-6) accumulation induced by intraperitoneal infection with the gram-positive bacterium *Listeria monocytogenes*. Although an important role for α2β1 on monocytes and inflammatory T cells in the process of migration to sites of inflammation had been established,[2] the high level of expression of α2β1 on



mast cells and its requirement in innate immune responses were not previously appreciated. The mast cell defect in α2β1 deficiency appears to be one of cell activation rather than of development, because peritoneal mast cell number, size, and granularity are comparable in wild-type and $\alpha2\beta1^{-/-}$ mice, and the nonspecific secretagogue compound 48/80 causes degranulation identically in mast cells from the 2 strains. As with all good experiments, the findings published in this paper suggest several new, important problems for understanding how mast cells contribute to host defense. The mast cell receptors for *Listeria* and zymosan, a derivative of the fungal cell wall that also induces PMN influx into the peritoneum in an α2β1-dependent fashion, are not known. The relevant ligand for the α2β1 integrin likewise is not clear. There is precedent for the possibility of synergy between integrin ligation and other signaling receptors in both the anchorage dependence of growth of many cell types[3] and the adhesion-dependent activation of PMNs in response to inflammatory stimuli,[4] but no understanding of whether and how crosstalk between bacterial and matrix protein signals might work in mast cells. Finally, Edelson et al show that early dissemination of *Listeria* infection is enhanced by the absence of α2β1 integrin but not of mast cells. This clearly demonstrates that α2β1 function on a cell type in addition to the mast cell is important in early control of infection. There are more surprises yet to come as the role for this integrin in innate immunity and host defense is discovered.

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1. Malaviya R, Abraham SN. Mast cell modulation of immune responses to bacteria. Immunol Rev. 2001; 179:16-24.
2. Dustin ML, de Fougerolles AR. Reprograming T cells: the role of extracellular matrix in coordination of T cell activation and migration. Curr Opin Immunol. 2001;13:286-290.
3. Schwartz MA, Ginsberg MH. Networks and crosstalk: integrin signalling spreads. Nat Cell Biol. 2002;4:E65-68.
4. Berton G, Lowell CA. Integrin signalling in neutrophils and macrophages. Cellular Signalling. 1999; 11:621-635.

T cells in mouse follicular lymphoma

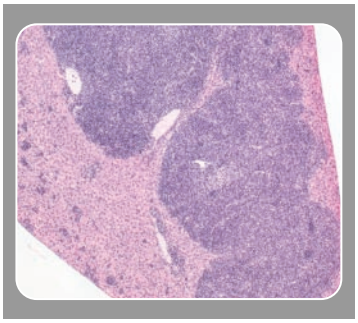
Common B-cell non-Hodgkin lymphomas (B-NHLs) arise by malignant transformation of defective germinal center (GC)–stage B cells.[1] These lymphomas include follicular lymphoma (FL) and more aggressive Burkitt (or Burkitt-variant) and diffuse large B-cell lymphomas. A characteristic t(14;18) is detectedin over 80% of FL, which causes overexpression of the *BCL2* cell survival gene by rearrangements with immunoglobulin (Ig) heavy chain locus control elements. Initially indolent, FL may transform to a more aggressive tumor with increasingly complex cytogenetics over time.

FL is also the most common B-cell lymphoma naturally arising in old mice and in *Eμ-Pim-1* transgenic mice. White pulp expansions of $sIgM^+/B220^+/CD19^+$ GC B cells usually begin in the spleen and may contain large (centroblasts, immunoblasts), small (centrocytes), or a mixture of large and small tumor cells that lose the usual GC spatial relationships. Unlike human FL, naturally occurring mouse FLs are not associated with *Bcl2* gene overexpression and do not display a typical follicular pattern. Despite several attempts, a *BCL2*-based model of FL has not been generated in mice, until now.

In this issue of *Blood*, Egle and colleagues (page 2276) describe a new model of FL by *Bcl2* overexpression using *VavP* control sequences. About 15% to 25% of mice developed a syndrome resembling autoimmune glomerulonephritis that was strain dependent. However, 37% to 50% of mice developed FL by 18 months of age following a florid GC hyperplasia.[2] Other hematologic tumors occurred at lower frequencies, including plasma cell tumors, lymphoblastic or large B-cell lymphoma, thymic lymphoma, and histiocytic sarcoma. Interestingly, levels of the *Bcl2* transgene expression were independent of lymphomagenesis; rather, $CD4^+$ T-cell help appeared essential for FL.

There are several exciting features in this valuable genetic model of human FL. The key seems to be panlymphoid *Bcl2* expression and time, which yield increased numbers of $CD4^+$ T cells that support robust GC B-cell expansions. Antigenic stimulation through surface Ig (sIg), with associated somatic hypermutation (SHM), has been described previously in human FL but not in mouse FL, which usually lacks

SHM and GC-signature Bcl6 protein expression.[3] Egle and colleagues show that antigenic selection is ongoing in this model and that the FL cells express the proliferating cell nuclear antigen (PCNA) GC-signature marker, features similar to human FL. Furthermore, Egle et al suggest that increased $CD4^+$ T cells in *VavP-Bcl2*, but not *Eμ-Bcl2*, transgenic mice support the premalignant GC expansion required to generate enough apoptosis-resistant B cells for a secondary transforming mutation. If this hy-



pothesis is correct, why are T-cell expansions not part of human follicular lymphomagenesis? Is there a T-cell help mechanism in human GCs that is so powerful that it obviates the need for excess $CD4^+$ T cells beyond those usually present? And what are the additional genetic/epigenetic mistakes that complement *Bcl2* overexpression to cause mouse FL? Do they have similar counterparts in human FL? This model, and one other that causes a spectrum of GC-based B-cell malignancies by overexpression of the *TCL1* oncogene in both B and T cells,[4] provide systems for determining some of the most difficult mechanisms in early GC B-cell transformation.

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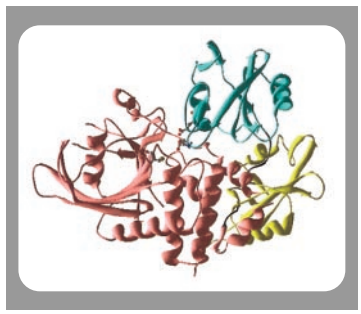
1. Kuppers R, Klein U, Hansmann ML, Rajewsky K. Cellular origin of human B-cell lymphomas. N Engl J Med. 1999;341:1520-1529.
2. Morse HC III, Anver MR, Fredrickson TN, et al. Bethesda proposals for classification of lymphoid neoplasms in mice. Blood. 2002;100:246-258.
3. Stamatopoulos K, Kosmas C, Belessi C, Stavroyianni N, Kyriazopoulos P, Papadaki T. Molecular insights into the immunopathogenesis of follicular lymphoma. Immunol Today. 2000;21:298-305.
4. Hoyer KK, French SW, Turner DE, et al. Dysregulated TCL1 promotes multiple classes of mature B cell lymphoma. Proc Natl Acad Sci U S A. 2002;99:14392-14397.

Mutated SHP and AML in leukemias

SHP-2 is a cytoplasmic tyrosine phosphatase with 2 src homology 2 (SH2) domains that was identified about 10 years ago and, most interestingly, acts to promote signal relay through the Ras-Erk pathway that plays a central role in cell proliferation and differentiation.[1,2] Although it remains unclear how a phosphatase is positively required for promotion of the Ras pathway, this notion was strikingly illustrated by identification of germline mutations in *PTPN11*, the gene coding for SHP-2, in patients with Noonan syndrome (NS) with cardiac and skeletal defects.[3] The autosomal dominant mutations identified cause amino acid substitutions that apparently disrupt an autoinhibitory interaction of the N-terminal of SH2 (SH2-N) domain with the PTPase domain, leading to expression of an excessively active phosphatase. More recently, somatic *PTPN11* mutations of a similar pattern were detected in patients with juvenile myelomonocytic leukemia (JMML) as well as in patients with myelodysplastic syndrome (MDS) and patients with de novo acute myeloid leukemia (AML).[4] In this issue of *Blood*, Loh and colleagues (page 2325) report an independent identification of somatic mutations in the SH2-N domain of SHP-2 in JMML specimens. Similar to those identified in patients with NS, the somatic mutations found in patients with JMML are clustered on the SH2-N and PTPase interaction surface, with D61Y and E76K most frequently detected. Furthermore, both groups found that mutations in *PTPN11*, *RAS*, and *NF1* are mutually exclusive in JMML. Together, these results identify SHP-2 as a first oncogenic tyrosine phosphatase in myeloid leukemias and suggest that the mutant SHP-2 molecule apparently promotes malignant cell proliferation by deregulating the Ras and possibly other signaling pathways. Preliminary functional analysis data suggest that the expression of mutant SHP-2 may or may not directly influence the Erk activation status. Clearly, more work is needed to fully understand the molecular mechanisms.

Somatically acquired mutations have also been detected in a number of genes coding for transcription factors.[5] In this issue of *Blood*, Harada and colleagues (page 2316) report identification of a new type of mutation in the *AML1/RUNX1* gene in patients with MDS and patients with AML. Previous publications by this group and others demonstrated somatic mutations in *AML1/RUNX1* that were localized to the N-terminal region, particularly in the DNA-binding Runt homology domain (RHD). The present study extended the previous work of



the investigators by detecting frame-shift mutations in the C-terminal part of the transcription factor, mainly in patients with MDS with refractory anemia with excess blast (RAEB), RAEB in transformation (RAEBt), and AML following MDS. Functional analysis using a gene-reporter assay demonstrated that all the C-terminal mutations abolished its *trans*-activation capacity and thus that these mutants could be viewed as dominant-negative suppressors of wild-type AML1 protein.

In sum, mechanisms have been used in leukemogenesis that alter the cell regulation machinery either in cytoplasmic signaling