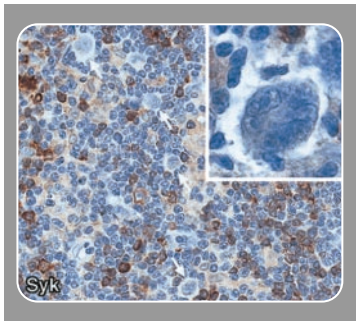
1. Caligiuri M, Strout M, Schichman S, et al. Partial tandem duplication of *ALL1* as a recurrent molecular defect in acute myeloid leukemia with trisomy 11. Cancer Res. 1996;56:1418-1425.
2. Nakamura T, Mori T, Tada S, et al. ALL-1 is a histone methyltransferase that assembles a supercomplex of proteins involved in transcriptional regulation. Mol Cell. 2002;10:1119-1128.
3. So CW, Lin M, Ayton PM, et al. Dimerization contributes to oncogenic activation of MLL chimeras in acute leukemias. Cancer Cell. 2003;4:99-110.
4. Martin ME, Milne TA, Bloyer S, et al. Dimerization of MLL fusion proteins immortalizes hematopoietic cells. Cancer Cell. 2003;4:197-207.
5. Look AT. Oncogenic transcription factors in human acute leukemias. Science. 1997;278:1059-1064.

Hidden identity of Hodgkin/Reed-Sternberg cells

The identity of Hodgkin/Reed-Sternberg (H/RS) cells has been a subject of intense investigation. Only recently has there been conclusive evidence that H/RS cells are derived from germinal center B cells in the large majority of Hodgkin lymphomas (HL).[1] However, H/RS cells usually do not express membrane markers characteristic of B cells. The study by Marafioti and colleagues (page 188) sheds light on the hidden B-cell identity of H/RS cells. They found that these cells lack several intracellular signaling molecules found in normal B cells and most B-cell lymphomas. Specifically, the protein spleen tyrosine kinase (Syk), the B-cell linker protein (BLNK), and phospholipsase γ2 (PLC-γ2) were consistently absent from H/RS cells in classical HL. In contrast, lymphocytic and/or histiocytic (L&H) variants of H/RS cells in all cases of nodular lymphocyte predominance HL (NLPHL) expressed these B-cell–specific signaling molecules. This finding is in agreement with the known biologic and clinical differences between classical HL and NLPHL. In NLPHL, L&H variants of H/RS cells retain many of the characteristics of normal germinal B cells, including ongoing hypermutation of immunoglobulin (Ig) genes.

The current study not only enhances our understanding of the biology of HL, but can also prove to be of diagnostic value. The different expression patterns of B-cell signaling molecules could facilitate the sometimes difficult morphologic distinction of NLPHL from lymphocyte-rich classical HL, which has a clinical behavior more like other types of classical HL.[2] Lyn kinase, another B-cell signaling molecule, was absent in 75% of classical HL and in a



similar proportion (15 of 19) of NLPHL. It will be interesting to learn whether this finding will help to distinguish NLPHL from progressively transformed germinal centers, a clinically benign condition that often precedes, follows, or coexists with NLPHL.

The study by Marafioti et al revealed heterogeneous expression of Lyn and Fyn Src kinases in classical HL. Other studies have shown selective loss of B-cell transcription factors. It would be interesting to learn whether this heterogeneity is associated with the variable presence of Epstein-Barr virus detected in H/RS cells in 40% to 50% of classical HL.[3] The possible association of Epstein-Barr virus with intracellular signaling molecules is not addressed in the current study. Correlations of heterogeneous activity of intracellular signaling molecules with responses to therapy and patient outcome are possible avenues of future research.

Now that Marafioti et al have shown that NLPHL expresses some signaling components used by the B-antigen cell receptor, one would like to know whether these pathways are active. Their expression could simply be a reflection of a particular transcriptional pathway, and the function of these proteins might be unnecessary for the growth of NLPHL cells. On the other hand, the presence of these signal transduction molecules could mean that their function is necessary to develop NLPHL. In order for Syk to activate PLCγ2, it is likely that the cells would also need to express a Tec family protein tyrosine kinase, which in normal B cells is Bruton tyrosine kinase (Btk). One would like to know whether Btk, or another Tec kinase, is expressed and activated in NLPHL. There are several ways that the roles of Btk, Syk, PLCγ2, and BLNK could be investigated in NLPHL. Phosphospecific antibodies that detect activated proteins could be used, although not all of these antibodies work well for immunohistochemistry. Cell lines derived from NLPHL[4] could also be studied with phosphospecific antibodies and inhibitors of Syk and PLCγ2 and perhaps siRNA to inhibit protein expression. If these proteins are necessary to develop NLPHL, then drugs that inhibit Syk, Btk, or PLCγ2 could be of therapeutic benefit.

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1. Kanzler H, Rajewsky K, Zhoa M, et al. Hodgkin disease: Hodgkin and Reed-Sternberg cells picked from histological sections show clonal immunglobulin gene rearrangements and appear to be derived from B cells at various stages of development. Proc Natl Acad Sci U S A. 1994;91:10962-10966.
2. Diehl V, Sextro M, Franklin J, et al. Clinical presentation, course, and prognostic factors in lymphocyte-predominant Hodgkin's diasease and lymphocyte-rich classical Hodgkin's disease: report from the European Task Force on Lymphocyte-Predominant Hodgkin's Disease. J Clin Oncol. 1999;17:776-783.
3. Sleckman BG, Mauch PM, Ambinder RF, et al. Epstein-Barr virus in Hodgkin's disease: correlation of risk factors with molecular evidence of viral infection. Cancer Epidemiol Biomarkers Prev. 1998;7:1117-1121.
4. Poppema S, De Jong B, Atmosoerodjo J, Idenburg V,Visser L, De Ley L. Morphologic, immunologic, enzyme histochemical and chromosomal analysis of a cell line derived from Hodgkin's disease: evidence for a B-cell origin of Reed-Sternberg cells. Cancer. 1985;55:683-690.