

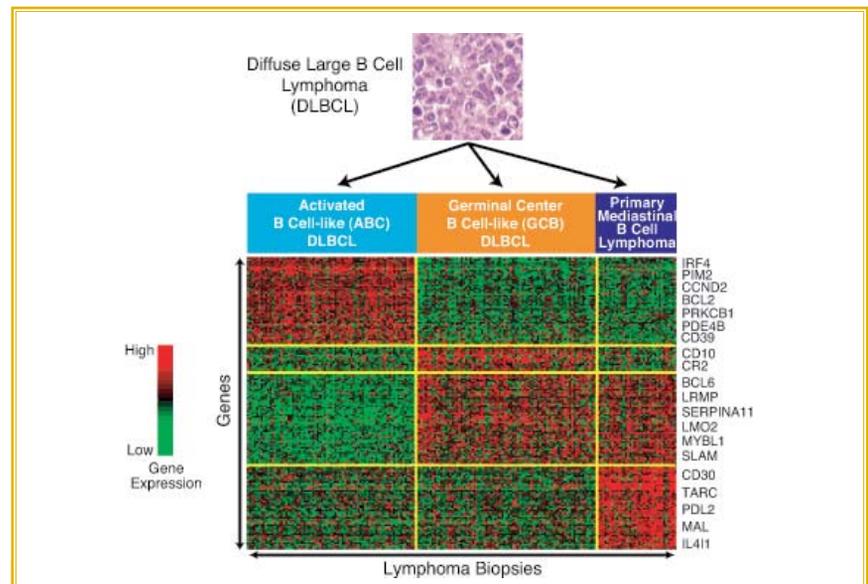
# Hitting the Target

Researchers have identified a possible target for treating the most aggressive form of lymphoma.

Single genetic mutations and, more commonly, combinations of mutations lead to the development of cancers such as lymphoma—a cancer of the blood that arises from infection-fighting white blood cells. Diffuse large B cell lymphoma (DLBCL), a type of non-Hodgkin's lymphoma, is the most common form of this disease and currently has a dismally low cure rate. There are three subtypes of DLBCL, of which the activated B cell-like (ABC) lymphoma has the worst outcome with a three-year survival rate of just 40 percent.

However, researchers have identified a recurring genetic mutation that could lead to targeted therapies for ABC lymphoma patients. Mutations of the *MYD88* gene (normally involved in the immune response to invading microorganisms) are found in 39 percent of patients with the ABC subtype of DLBCL and could drive the growth of some lymphoma tumors by activating multiple signaling pathways associated with cancer. A study published in the December 22, 2010, issue of *Nature* from the laboratory of Louis Staudt, M.D., Ph.D., Deputy Chief of CCR's Metabolism Branch, reveals a mechanism whereby a single alteration in the MYD88 protein sequence can cause uncontrolled cellular signaling, leading to survival of malignant cells.

Dr. Staudt and colleagues have worked to identify proteins that play a role in the development of the ABC subtype as potential targets to improve the treatment of patients with this form of lymphoma. To identify these critical proteins, the researchers performed a screen in which thousands of genes were inactivated. They found that ABC lymphoma cells were killed when they inactivated the



Biopsies of diffuse large B cell lymphoma (DLBCL) reveal varying gene expression levels in activated B cell-like DLBCL, germinal center B cell-like DLBCL, and primary mediastinal B cell lymphoma.

genes encoding MYD88 and IRAK1, another cell signaling protein that works with MYD88.

The scientists then looked for specific mutations in *MYD88* that might explain the survival-dependence they observed. Sequencing of the *MYD88* gene in 382 lymphoma biopsy samples revealed that 29 percent of ABC lymphoma samples had the same mutation, which altered a single amino acid in the MYD88 protein, but this mutation was rare or absent in other lymphoma subtypes. The mutant form of *MYD88* sustained the survival of the ABC lymphoma cells while the non-mutated version did not, suggesting that mutations in the *MYD88* gene could play an important role in the development of ABC DLBCL.

The researchers then examined proteins that interact with MYD88 in lymphoma cells. The mutant form of MYD88 spontaneously assembled a protein complex that included IRAK1, identified in the genetic screen,

and a related protein, IRAK4. In this protein complex, IRAK4 functioned as an enzyme to modify IRAK1, which was required for the mutant MYD88 protein to promote lymphoma cell survival. This particular finding may hold promise for the treatment of lymphomas with MYD88 mutations since pharmaceutical companies are developing IRAK4 inhibitors for use in inflammatory and autoimmune diseases, noted Dr. Staudt.

“The results of this study may provide a method to identify patients with the ABC subtype of diffuse large B cell lymphoma whose tumors may depend upon MYD88 signaling,” said Dr. Staudt. “And these patients may one day benefit from therapies targeting this and other regulatory pathways that sustain the survival of these lymphoma cells.”

To learn more about Dr. Staudt's research, please visit his CCR Web site at <http://ccr.nci.nih.gov/staff/staff.asp?Name=staudt>.

(Image: L. Staudt, CCR)