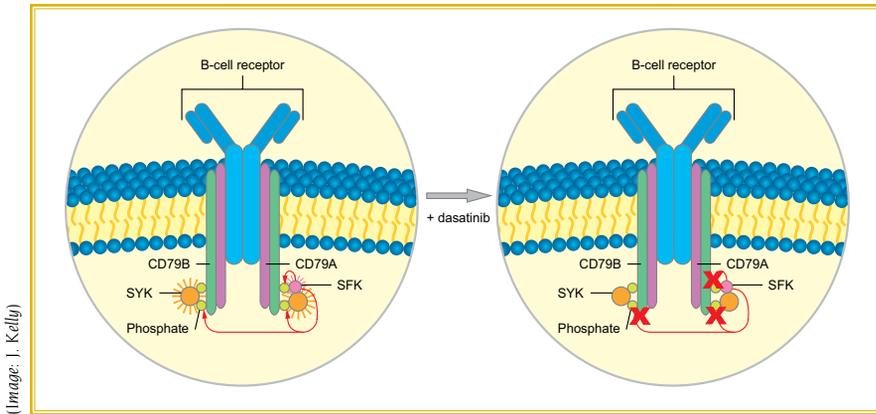


Sending the Right Signals

Mutations in B-cell receptor signaling pathways identify new molecular targets for the most common type of non-Hodgkin's lymphoma.



(Image: J. Kelly)

Dasatinib inhibits key signaling pathways in the activated B cell-like subtype of diffuse large B-cell lymphomas.

Diffuse large B-cell lymphomas (DLBCL), the most common type of non-Hodgkin's lymphoma, causes about 10,000 deaths every year in the United States, even though about half of all patients are cured with current regimens. There are different subtypes of DLBCL that vary biologically and have significantly different rates of patient survival following chemotherapy, with the activated B cell-like (ABC) subtype being the least responsive to current therapies. So Louis M. Staudt, M.D., Ph.D., Head of the Molecular Biology of Lymphoid Malignancies Section at CCR, and his team set out to find why patients with this subtype have such unfavorable outcomes and how treatment of this disease can be improved.

When a normal B cell recognizes a foreign substance, B-cell receptors (BCR) on the cell surface activate signaling pathways that trigger cell proliferation and survival. Mutations in signaling pathways have been

found in many types of cancer cells, and previous research has suggested that abnormal BCR signaling might contribute to the development of lymphomas. However, there wasn't any direct genetic or functional evidence to support this theory.

In the January 7, 2010 issue of *Nature*, Dr. Staudt and his colleagues reported a mechanism that promotes cell survival for lymphomas of the ABC subtype of DLBCL cells, thus identifying potential new targets for treatment of the disease. The team used a new approach—an Achilles heel screen—in which they used a technique called RNA interference to inactivate genes in ABC DLBCL cells and test their necessity for proliferation and survival. They determined critical points in the BCR signaling pathway that affect the survival of these lymphoma cells and found that interfering with several individual components of this pathway caused lymphoma cells to die. Thus, they came to the conclusion

that ongoing BCR signaling (chronic active signaling) is necessary for cell survival of the ABC DLBCL subtype.

The researchers then looked for mutations in DLBCL tumors in genes that encode these signaling pathway components and found that about 20 percent of ABC subtype tumors had mutations in a BCR signaling component known as CD79B. The mutations increased BCR signaling by blocking a braking process that normally turns off the pathway in response to inhibitory signals. "These mutations we found in the cancer were very juicy, in a way," said Dr. Staudt. "They hit critical amino acids responsible for B-cell receptor signaling, which clearly told us that this receptor was functionally mutated in these lymphomas. That was a genetic smoking gun that the B-cell receptor was important."

This study sets the stage for testing agents that target components of the BCR signaling pathway as new therapeutic strategies for DLBCL. In fact, the researchers have already found that dasatinib, a drug that is approved for the treatment of chronic myelogenous leukemia, could turn off BCR signaling by inhibiting the activity of a protein called BTK, thereby killing ABC subtype DLBCL cells that exhibit chronic active BCR signaling.

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