Scientists identify possible gene target for treating a form of lymphoma

December 22 2010

Researchers have identified a mutation in a gene that could lead to targeted therapies for certain lymphoma patients whose cure rates are currently poor. Mutation of the MYD88 gene was found to be one of the most frequent genetic abnormalities in a form of cancer known as diffuse large B cell lymphoma. MYD88 encodes a protein that is crucial for the normal immune response to invading microorganisms. New experiments show a mutation in the MYD88 protein sequence can cause uncontrolled cellular signaling, leading to survival of malignant cells. The study, led by researchers from the National Cancer Institute (NCI), part of the National Institutes of Health, appeared online in *Nature*, Dec. 22, 2010.

Single mutations, or more often, combinations of gene mutations, can lead to the development of cancers such as lymphoma. Lymphoma is a cancer of the blood that arises from infection-fighting white blood cells. Diffuse large B cell lymphoma, a type of non-Hodgkin's lymphoma, is the most common form of this disease. There are three subtypes of diffuse large B cell lymphoma, of which the activated B cell-like (ABC) form has the poorest three-year survival outcome of 40 percent.

Louis M. Staudt, M.D., Ph.D., Metabolism Branch, Center for Cancer Research, NCI, and colleagues, have worked to identify proteins that play a role in the development of the ABC subtype because these proteins may provide targets to improve the treatment of patients with this form of lymphoma. To identify these critical proteins, the researchers performed a genetic screen in which thousands of genes

were inactivated. They found that ABC lymphoma cells were killed when they inactivated the genes encoding MYD88 and IRAK1, another cell signaling protein that works with MYD88.

The scientists then looked for genetic mutations that might explain why the ABC lymphoma cells were so dependent upon MYD88. 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 but the non-mutated version did not, suggesting that mutations in the MYD88 gene could play an important role in the development of ABC diffuse large B cell lymphomas.

To understand how MYD88 might promote ABC lymphoma cell survival, the researchers examined proteins that interact with MYD88 in the 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 have direct therapeutic implications since pharmaceutical companies are developing IRAK4 inhibitors for use in inflammatory and autoimmune diseases, according to the scientists.

“We believe 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 and who may therefore benefit from therapies targeting IRAK4 alone or in combination with agents targeting other regulatory pathways that sustain the survival of these lymphoma cells,” said Staudt.