Scientists find key pathway implicated in progression of childhood cancer

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A protein crucial for the immune response appears to be a key player in the progression of a devastating form of childhood leukemia called T-cell acute lymphoblastic leukemia (T-ALL). Suppressing the activity of the protein kills the leukemic cells, the study shows, opening a potential avenue to new drugs that could prevent progression of the disease.

Led by Iannis Aifantis, PhD, associate professor of pathology and director of the Cancer Stem Cell Program at the NYU Cancer Institute at NYU Langone Medical Center, and colleagues at the Institute Municipal d'Investigacions Mediques in Barcelona, Spain, the new study appears in the September 14, 2010, issue of *Cancer Cell*. These molecular detectives discovered the protein by picking up on a bit of cross-talk, or conversation, between two unrelated genes.

"We are very excited about this discovery because small molecule drugs that block this protein are already in development," said Aifantis, who is also a Howard Hughes Medical Institute Early Career Scientist. "We plan to continue to study these inhibitors in the laboratory with the aim of evaluating the feasibility of testing such drugs in patients.

Despite great strides in treating childhood leukemia, T-ALL, poses special challenges because of the high risk of leukemic cells invading the brain and spinal cord of children who relapse. T-ALL, a blood-borne cancer in which the bone marrow makes too many lymphocytes, or white blood cells, strikes several hundred children and adolescents in the U.S. annually. While more than 90 percent initially go into remission through

a combination of chemotherapy and radiation, up to one third of this group eventually relapse.

Previous research had strongly implicated a well-known oncogene, or cancer-causing gene, called Notch1 in the initiation and progression of T-ALL in patients. Certain kinds of mutations in this gene have been found in nearly half of T-ALL patients and current estimates suggest that the gene's regulatory influence might be implicated in nearly 90 percent of cases.

In the new study, the researchers found that Notch targeted a protein called NF-kB (short for nuclear factor kB), an important transcription factor that regulates genes involved in cell division and the immune response. Transcription factors bind to the DNA of genes, thereby activating them. Previous studies had suggested that cross talk between Notch and NF-kB occurred, but the new study reveals the molecular characters involved in the cross talk, and shows that blocking NF-kB eliminated leukemic cells carrying activating Notch mutations.

The researchers then found that the way that Notch1 can induce NF-kB signaling is by suppressing the expression of an enzyme called CYLD, a negative regulator of the NF-kB pathway. In other words, the enzyme normally shuts down the pathway of genes regulated by NF-kB.

"Presently, drugs that inhibit NF-kB are already in development and some of them are being tested in humans for inflammatory diseases," said Dr. Aifantis, "If used for patients with T-ALL leukemia, such drugs could be used alone or in combination with more established protocols like chemotherapy and radiation."

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