Study finds mutations linked to relapse of childhood leukemia

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After an intensive three-year hunt through the genome, medical researchers have pinpointed mutations that leads to drug resistance and relapse in the most common type of childhood cancer—the first time anyone has linked the disease's reemergence to specific genetic anomalies.

The discovery, co-lead by William L. Carroll, MD, director of NYU Langone Medical Center's Cancer Institute, is reported in a study published online February 3, 2013, in Nature Genetics.

"There has been no progress in curing children who relapse, in spite of giving them very high doses of chemotherapy and bone marrow transplants," said Dr. Carroll.

The discovery suggests how scientists may be able to thwart a dangerous form of acute lymphoblastic leukemia, a rapidly progressing blood-borne cancer that strikes about 6,000 people in the United States every year and accounts for more than one in four pediatric cancers. Eventually, such information could help doctors detect the early emergence of chemotherapy-resistant leukemia cells in patients and switch to a different treatment strategy before the disease can fully reassert itself.

In acute lymphoblastic leukemia, abbreviated ALL, the body's bone marrow produces an abnormally large number of lymphocytes, or white blood cells. Improved treatments have increased the overall cure rate to roughly 80 percent. But Dr. Carroll says the prognosis is especially dire

for some 20 percent of patients who relapse.

Medical researchers have suspected that the reemergence of disease could be due to drug resistance, but previous efforts had not uncovered any definitive pathway. For the new study, led by Dr. Carroll and graduate student Julia Meyer, researchers at five U.S. institutions spent three years analyzing multiple bone marrow samples from pediatric ALL patients for more clues to the disease's progression.

With the help of the Children's Oncology Group, a multi-institutional clinical trials consortium supported by the National Cancer Institute, the researchers analyzed the entire transcriptome—or the full sequence of RNA —from 10 children with pediatric B lymphoblastic leukemia, the most common subtype of ALL. RNA is an essential intermediary in the cellular process that uses DNA blueprints to assemble specific proteins, thus a leukemia transcriptome gives researchers a view of all active genes within the cancerous cells.

For each patient, the team pieced together a complete sequence of RNA extracted from the bone marrow at three time points: at diagnosis, during remission, and upon relapse some months or years later. All told, the project required the researchers to sequence, or spell out, 100 billion letters of RNA. By comparing the before and after sequences, the team found that each patient had acquired between one and six mutations that changed the genetic code over the course of the disease. In some cases researchers were able to detect these mutations in a very small subset (0.01 percent) of the tissue samples at diagnosis so that these cells likely expanded because their drug resistant properties provided the leukemia cells with a survival advantage.

In all, the team documented 20 relapse-specific mutations—none of which had previously been implicated in ALL recurrences. Intriguingly, two patients harbored a mutation in the same gene, NT5C2, which

encodes a protein that normally regulates some building blocks used to construct DNA but also can degrade an important class of drugs called purine analogues used in ALL therapy.

When the researchers fully sequenced the NT5C2 gene in 61 other cases in which pediatric ALL patients had relapsed, they found five more mutations that altered the gene's coding region. Further experiments suggested that these NT5C2 mutations all increased the protein's enzymatic activity, making the cancer cells more resistant to a chemotherapy treatment designed to force the cells to kill themselves. All seven patients with NT5C2 mutations relapsed within three years of the initial diagnosis—an early, particularly hard-to-treat re-emergence likely mediated by the drug resistance.

Armed with the new knowledge, Dr. Carroll says doctors may be better equipped to identify patients likely to relapse. "We plan to test the feasibility of screening patients during therapy using sophisticated sequencing technology to pick up low-level mutations in NT5C2 and other genes indicating that a mutant clone is growing," he says. His team is researching whether that advance warning could allow doctors to administer separate drugs to beat back the cancer cells, and is also working on a strategy to directly inhibit the mutant enzyme.

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