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St. Jude identifies genomic causes of a certain type of leukemia relapse

New study finds the majority of acute lymphoblastic leukemia relapse cases arise from a cell already present at the time of diagnosis

Scientists at St. Jude Children's Research Hospital have identified distinctive genetic changes in the cancer cells of children with acute lymphoblastic leukemia (ALL) that cause relapse. The finding offers a pathway to designing treatments for ALL relapse in children and, ultimately, in adults.

The most common childhood cancer, ALL affects thousands of children annually in the United States. Although more than 80 percent of ALL cases are cured, relapse is a significant problem, with only 30 percent of children with relapsed ALL surviving.

Previous studies had found some evidence for genetic differences between the cancer cells of ALL patients at initial diagnosis and those who relapsed. That information was limited, and there had never been a broad comparison of the entire genomes of ALL at initial diagnosis and at subsequent relapse.

In the study that appears in the Nov. 28, 2008, issue of the journal *Science*, St. Jude researchers compared the genomes of the cancer cells of 61 childhood ALL patients when they were initially diagnosed and after they had relapsed. The investigators used millions of genetic markers—characteristic genetic variations called single nucleotide polymorphisms—as guideposts to pinpoint genetic changes characteristic of relapsed cells. Using these genetic markers, the researchers analyzed all of the cells' chromosomes to look for genetic changes called copy number abnormalities specific to relapsed cells. These changes are considered a major type of damaging gene alterations in ALL.

"In more than 90 percent of the cases, we found differences in the genetic alterations present at the time of diagnosis and at the time of relapse," said Charles Mullighan, M.D., Ph.D.,

assistant member in the St. Jude Department of Pathology and the paper's first author. "Examining the new changes that are arising at relapse tells us a lot about the individual genetic lesions that might confer resistance to treatment and be responsible for relapse."

According to the researchers, the relapse-related genetic changes commonly disrupted the machinery by which white blood cells called B cells mature and proliferate. Importantly, the relapse-related genetic changes only infrequently involved genes directly regulating the responsiveness to anti-cancer drugs.

The analysis also indicated that in most cases, the cancer cells responsible for relapse were related to those that originally gave rise to the cancer. Those relapse cells were present at low levels at diagnosis, the scientists' analysis indicated. However, in a few cases, the relapse cells evolved from genetically distinct cells, indicating that the relapsed leukemia was actually an entirely new cancer.

"The key finding in our work is that in the majority of cases, relapse is arising from a cell already present at the time of diagnosis," said James Downing, M.D., St. Jude Scientific Director, chair of the Department of Pathology and the paper's senior author. "That cell is selected for during treatment and then subsequently emerges as basis for relapse."

"The second key point is that we have found a large number of new genetic alterations that had not been previously identified as new targets of copy number changes at the time of relapse," Mullighan added.

Mullighan emphasized that the findings do not mean immediate treatments for ALL relapse. "But, this is a very important starting point because we have identified several key pathways that are the most common targets of new genetic changes at the time of relapse," he said.

Identification of these relapse pathways will lead to understanding of the biological machinery of relapse, and ultimately to drugs that target that machinery. Such studies of the relapse machinery are now underway at St. Jude.

In other further studies, the researchers are also looking for other relapse-related genetic alterations besides copy number abnormalities. They are also applying their findings to adult ALL, in which relapse is a more significant problem than in the childhood disease.

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Other authors of this paper include Letha Phillips, Xiaoping Su, Jing Ma, Christopher Miller and Sheila Shurtleff.

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St. Jude Children's Research Hospital

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