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Existing drugs offer new treatment options for high-risk childhood leukemia subtype

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Scientists have identified new genetic alterations underlying a high-risk subtype of the most common childhood cancer that could be effectively targeted with existing leukemia therapies.

The study focused on a subtype of acute lymphoblastic leukemia (ALL) known as Philadelphia chromosome-like ALL (Ph-like ALL). This subgroup accounts for as much as 15 percent of childhood ALL that is associated with a high risk of relapse and a poor outcome. The genetic changes driving the disease were previously unknown for about half of all patients with Ph-like ALL. The work identified new alterations in genes that regulate how cells grow and proliferate. St. Jude Children's Research Hospital investigators led the research, which appears in the online edition of the journal *Cancer Cell*.

Investigators also showed that the leukemia cells were sensitive to several targeted therapeutic agents, imatinib and dasatinib, which are already being used against other leukemias, but not this subtype. The findings suggest patients with Ph-like ALL may benefit from the addition of these drugs to current chemotherapy regimens.

"One of the next steps will be to continue work on laboratory tests to rapidly identify patients whose cancer cells carry these alterations and to develop clinical trials to test targeted therapies," said Charles Mullighan, M.D., Ph.D., an associate member of the St. Jude Department of Pathology, and a corresponding author of the study.

The study involved sequencing the RNA of cancer cells from 15 patients with Ph-like ALL and whole genome sequencing of two of those patients. Whole genome sequencing involves deciphering the DNA molecule, which contains the complete set of instructions for building and maintaining life. Cells use RNA to translate DNA's instructions into proteins. Sequencing RNA provides a snapshot of gene activity in a cell.

The work was part of the National Cancer Institute's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, which aims to use genomics to identify therapeutic targets and spur development of more effective treatments for childhood cancer. NCI is part of the National Institutes of Health. The collaboration included investigators from St. Jude, the Children's Oncology Group and the British Columbia Genome Sciences Center.

"This work is another example of how a detailed analysis of the genetic changes present in cancer cells can identify the changes that are critical for cancer cells to escape normal growth controls and allow them to resist standard chemotherapy treatments, but also serve as an Achilles' heel that can be attacked by drugs targeted at these genetic changes. It's also important to recognize that work like this is only possible because patients with ALL and their parents agreed to participate in clinical trials and linked studies about the genetics of cancer," said Stephen Hunger, M.D., a professor of pediatrics at the University of Colorado, chairman of the Children's Oncology Group ALL Committee and a corresponding author of the study.

ALL is the most common childhood cancer. While approximately 90 percent of newly diagnosed ALL patients are cured with current treatments, only 63 percent of children with Ph-like ALL are alive and cancer-free after five years.

Ph-like ALL is named after a chromosomal rearrangement known as the

Philadelphia chromosome, which is associated with another subtype of ALL. The two subtypes share similar gene expression profiles, but patients with Ph-like ALL lack the fusion of the BCR and ABL1 genes that is a hallmark of Philadelphia-positive ALL.

To determine the genetic basis of Ph-like ALL, investigators performed transcriptome and whole genome sequencing on cancer cells from young patients with Ph-like ALL. Researchers found the 15 patients harbored genetic alterations, including mutations, chromosomal rearrangements or structural variations, which disrupted tyrosine kinase or cytokine receptor signaling. Kinases are enzymes that function as on-off switches in cells. Cytokine receptors regulate how cells respond to growth factors known as cytokines.

Researchers also found the leukemia cells carried additional mutations or deletions affecting IKZF1 and other genes involved in normal B cell development. "This supports the notion that many subtypes of ALL have at least two key pathways disrupted. One is a block in maturation of immature B cells and the other drives proliferation of those cells," Mullighan said.

When investigators screened another 436 young patients with high-risk B-cell ALL, they found some patients with Philadelphia-like ALL carried the same alterations. Those changes included the fusion of a gene named EBF1 to the tyrosine kinase gene PDGFRB. This study is the first to link the EBF1-PDGFRB fusion to cancer. Other fusions associated with ALL for the first time involved the genes STRN3-JAK2 and RANBP2-ABL1.

Researchers also showed that expression of EBF1-PDGFRB freed white blood cells from normal controls and allowed them to proliferate in the absence of growth factor. The addition of the tyrosine kinase inhibitors imatinib and dasatinib slowed proliferation and induced cell death.

When human Ph-like ALL cells expressing the NUP214-ABL1 rearrangement were transplanted into mice, the animals responded to treatment with dasatinib. Another mouse model of human Ph-like ALL that included a BCR-JAK2 fusion showed a dramatic reduction of leukemia cells following treatment with the JAK2 inhibitor, ruxolitinib. The drug is approved for use against other blood disorders with mutations in JAK2, a protein involved in cytokine signaling. Together these results suggest that although a wide range of alterations exist in Ph-like ALL, they converge on similar pathways that can be targeted with currently available ABL1 or JAK2 inhibitors.

"Although much work remains to be done, these results suggest most patients with this cancer subtype may respond to treatment with currently available tyrosine kinase inhibitors," said Kathryn Roberts, Ph.D., a St. Jude postdoctoral fellow. She and Ryan Morin, Ph.D., of the BC Cancer Agency, Vancouver, Canada, are the study's first authors.

Provided by St. Jude Children's Research Hospital