Mutant genes in high-risk childhood leukemias identified

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A research team has pinpointed a new class of gene mutations, which identify cases of childhood acute lymphoblastic leukemia (ALL) that have a high risk of relapse and death. The finding suggests specific drugs that could treat this high-risk leukemia subtype in children, particularly because such drugs are already in clinical trials for similar blood diseases in adults.

While the cure rate in pediatric ALL has reached about 85 percent, the remaining high-risk cases have proven especially intractable because they arise from different, unidentified genetic mutations.

Discovery of the mutations was led by scientists from St. Jude Children's Research Hospital, the Children's Oncology Group (COG), the University of New Mexico Cancer Research and Treatment Center, Albuquerque, N.M., and the National Cancer Institute (NCI), part of the National Institutes of Health (NIH). This research was done as part of the NCI Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, which seeks to utilize the study of genomics to identify therapeutic targets in order to develop more effective treatments for childhood cancers. The article appears online May 18 in the early edition of the Proceedings of the National Academy of Sciences.

"We have made such great progress in curing children with ALL that the main challenge is now the remaining high-risk patients," said St. Jude Scientific Director, James Downing, M.D., a co-senior author of the

study. "We still do not know how to accurately identify these patients and effectively treat them to provide the highest chance for a cure. The problem is that this high-risk group is likely a heterogeneous mixture of biologic subtypes."

The new study builds on the researchers' previous genetic analysis of the leukemic cells from pediatric ALL patients.

"The findings from our previous studies have hinted that some high-risk ALL cases might arise from mutations in genes that produce enzymes called kinases, which function as biological on-off switches in cells," said Charles Mullighan, M.D., Ph.D., assistant member in the St. Jude Department of Pathology and a co-first author of the study. "Such mutations would cause those kinases to be stuck in the on position, triggering the uncontrolled proliferation of white blood cells that is seen in leukemia."

Thus, the researchers began to analyze the genetic sequences of many kinases known to be components of the proliferation machinery of white blood cells. The team analyzed the leukemic cells from 187 patients with high-risk ALL. That analysis revealed mutations in about 10 percent of the cases in a family of protein kinases called JAK, whose members were also known to be mutated in other types of leukemias and related diseases.

"Further studies of these mutant JAK proteins revealed that the changes in their molecular structures could switch them on to drive the blood cell proliferation that is characteristic of ALL," said Stephen Hunger, M.D., chairman of the COG ALL committee and a co-senior author of the study. "What's more, in test tube studies, we found that drugs blocking the activation of the mutant JAK kinases prevented uncontrolled growth suggesting that drugs that target JAK proteins might be effective in this subtype of ALL."

The researchers discovered, in some high-risk ALL patients, that mutations in JAK appeared to work in concert with another mutation—in the gene IKZF1—which they had earlier found to underlie such cases.

"Our studies of these leukemia subtypes indicate that leukemia is not necessarily a single-cause disease," said Cheryl Willman, M.D., director and CEO of the University of New Mexico Cancer Research and Treatment Center and a co-senior author of the study. "A patient may have multiple different genetic lesions that target different cellular pathways to induce leukemia. Thus, it is very important to develop new therapies that target these specific mutations, and our discovery of JAK as target now allows us to begin to develop clinical trials with JAK inhibitors for children and adults with this form of disease."

In further studies, the researchers plan to identify mutations in kinase genes and other enzymes that underlie high-risk ALL, as well as explore how these abnormalities might work together to drive the cancers.

The discovery that mutations in JAK underlie some cases of high-risk ALL is enough to warrant clinical trials of inhibitory drugs to treat such cancers.

"JAK-inhibiting drugs are now moving into clinical trials for treatment of such adult myeloproliferative diseases as polycthemia vera, essential thrombocytosis and primary myelofibrosis," Downing said. "We expect that there will soon be initial clinical studies to assess the safety and effectiveness of these drugs in children with relapsed ALL in which JAK mutations have been identified within their leukemic cells."

Such studies would be coordinated by the COG, an international clinical trial cooperative group supported by the NCI.

Source: St. Jude Children's Research Hospital