Newly identified DNA repair defect linked to increased risk of leukemia relapse

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A newly identified defect in a DNA repair system might leave some young leukemia patients less likely to benefit from a key chemotherapy drug, possibly putting them at greater risk of relapse. The problem was identified in a study led by St. Jude Children's Research Hospital scientists.

The study's findings offer a potential new marker to help identify acute lymphoblastic leukemia (ALL) patients who are at higher risk of having their cancer return and thus are candidates for more tailored therapies. The research was published in the September 25 online edition of the scientific journal Nature Medicine.

The work focused on a protein named MSH2, which is involved in DNA repair. DNA is the molecule that carries instructions for building and sustaining life. Cell division requires DNA synthesis. The DNA repair system helps correct errors in DNA production. The DNA repair proteins are also involved in how some chemotherapy agents kill leukemia cells.

In this study, investigators discovered a new mechanism responsible for low MSH2 levels in about 11 percent of pediatric ALL and in several adult cancers. Researchers also found low MSH2 levels were associated with leukemia resistance to the thiopurine medications, including mercaptopurine, a drug all children with ALL receive.

"If confirmed, this work suggests a patient's MSH2 status might

someday be used to guide treatment," said Barthelemy Diouf, Ph.D., the first author. He is a postdoctoral fellow in the laboratory of William Evans, Pharm.D., the paper's senior author. Evans is chief executive officer and director of St. Jude.

In the U.S., ALL is diagnosed in about 3,000 children annually, making it the nation's most common childhood cancer. It is also one of modern medicine's success stories. At St. Jude, 90 percent of young ALL patients are now cured. This study reflects ongoing efforts to understand why treatment sometimes fails.

The research built on earlier work from the laboratory of Evans and others that linked a deficit of MSH2 with an increased risk of certain cancers and resistance to mercaptopurine, a drug that is the backbone of leukemia treatment.

In this study, scientists found that 11 percent of 90 newly diagnosed pediatric ALL patients had low or undetectable levels of the MSH2 protein.

Ten years after an ALL diagnosis, children with low MSH2 protein levels were less likely to be alive and four times more likely to have suffered relapses. The comparison included 97 patients treated in a St. Jude study called Total XV, which ended in 2007. Sixteen patients had leukemia with low MSH2 levels. The analysis took other factors into account, including a patient's age and early treatment response, which are associated with high-risk ALL. The results suggest MSH2 protein levels might help identify a new group of high-risk patients.

Further work revealed no evidence of problems in the MSH2 gene itself, so scientists expanded their search for why some patients had low MSH2 levels in their leukemia cells. Researchers looked for changes in the makeup of eight genes known or suspected of playing a role in the

breakdown of MSH2. To do that, they screened DNA from 69 of the 90 newly diagnosed ALL patients at nearly 1 million spots in the genome.

The research showed each patient was missing at least one of the four genes that regulate MSH2 degradation. "MSH2 was still made, but the system to protect it from destruction had been impaired or eliminated, leading to more rapid breakdown of MSH2 and a crippled system for fixing DNA," Evans said. The missing genes were FRAP1, HERC1, PRKCZ and PIK3C2B.

A check of leukemia cells from another group of St. Jude ALL patients found that about 12 percent, or 21 of the 170 children, were missing at least one of the same genes. A search of public databases found one or more of the same genes deleted in 13.5 percent of sporadic colorectal cancer patients and 16 percent of adults with ALL.

Evans noted that low MSH2 levels did not increase resistance to other drugs used to treat ALL. "In the future, we may want to intensify use of other therapies," he said.

Provided by St. Jude Children's Research Hospital