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Study yields new strategy against high-risk leukemia

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August 29, 2013) St. Jude Children's Research Hospital scientists have identified a protein that certain high-risk acute lymphoblastic leukemia (ALL) cells need to survive and have used that knowledge to fashion a more effective method of killing tumor cells. The findings appear in the August 29 edition of the journal *Blood*.

The work focused on Philadelphia chromosome-positive ALL (Ph-positive ALL), a high-risk cancer that accounts for about 40 percent of ALL in adults and about 5 percent in children. The disease is named for a chromosomal rearrangement that brings together pieces of the BCR and ABL genes. That leads to production of the BCR-ABL protein, which fuels the unchecked cell growth that is a hallmark of cancer.

In this study, researchers identified the protein MCL1 as the partner in crime of BCR-ABL. MCL1 is one of several proteins that can block the process of programmed cell death known as apoptosis. The body uses apoptosis to eliminate damaged, dangerous or unneeded cells. The research demonstrates that MCL1 is essential for preventing apoptosis of leukemia cells.

Investigators combined drugs that reduce MCL1 levels in leukemia cells with a second drug that targets another protein that inhibits cell death. The pairing increased apoptosis in human leukemia cells growing in the laboratory.

"These findings suggest that disrupting the ability of leukemia cells to

produce MCL1 renders those cells vulnerable to other drugs," said corresponding author Joseph Opferman, Ph.D., an associate member of the St. Jude Department of Biochemistry. "That is exciting because we already have drugs like imatinib and other tyrosine kinase inhibitors that reduce MCL1 production in tumor cells, leaving those cells vulnerable to being pushed into death via apoptosis by other drugs already in development."

Tyrosine kinase inhibitors are designed to block the BCR-ABL protein. The drugs have revolutionized treatment of chronic myeloid leukemia (CML), which strikes adults and includes the same chromosomal rearrangement as Ph-positive ALL. But results of TKI treatment were less dramatic for adults and children with Ph-positive ALL, and drug resistance remains a problem.

For this study, researchers combined one of two tyrosine kinase inhibitors, imatinib or dasatnib, with the experimental drug navitoclax. The latter drug disrupts the ability of the proteins BCL-2 and BCL-XL to protect cancer cells from apoptosis. Along with MCL1, BCL-2 and BCL-XL are members of a family of proteins that regulate apoptosis. MCL1, BCL-2 and BCL-XL work to prevent cell death, even cancer cell death, by blocking the activity of proteins that promote the process.

Since MCL1 is elevated in a number of cancers and is associated with cancer-drug resistance, a similar two-drug approach might also enhance the effectiveness of tyrosine kinase inhibitors for treatment of other cancers. "We are very interested in pursuing this strategy," Opferman said.

Earlier discoveries made by the Opferman laboratory revealed that MCL-1 also protects heart health by preventing loss of heart muscle cells through apoptosis. "Together these findings suggest that MCL1 is a relevant target for cancer treatment, but efforts should focus on

diminishing the expression of MCL1, rather than completely eliminating its function," said first author Brian Koss, a staff scientist in Opferman's laboratory.

In this study, the investigators showed that MCL1 was required for cancer cell survival throughout the Ph-positive ALL disease process, beginning when white blood cells known as B lymphocytes were transformed from normal to tumor cells.

Scientists showed that deleting Mcl1 from the leukemia cells of mice blocked cancer's progression and turned the mice into long-term survivors.

Provided by St. Jude Children's Research Hospital