Targeting errant immune system enzyme kills myelodysplastic cells

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Scientists have successfully targeted a malfunctioning immune system enzyme to kill diseased cells from patients with myelodysplastic syndrome (MDS)—a blood disorder and precursor to leukemia.

Reporting their results July 8 in *Cancer Cell*, researchers say their successful laboratory tests in human MDS cells and mouse models of MDS provide a molecular target for designing new drugs to battle a syndrome with few effective treatments.

"There is an urgent need to develop new targeted therapies that can eliminate MDS-initiating clone cells and provide a durable therapeutic response," said Daniel Starczynowski, PhD, lead researcher and a member of the Division of Experimental Hematology and Cancer Biology at Cincinnati Children's Hospital Medical Center. "Not only does our research implicate errant immune system signaling in MDS cells, it strongly indicates that inhibiting the function of this hijacked immune pathway may become an effective treatment option for MDS."

MDS is a group of syndromes in which a person's immature blood cells (blood stem cells) do not mature into healthy red or white blood cells. Instead, the immature cells die off in the bone marrow or blood, leaving an insufficient number of healthy cells in the body. This can cause infections, anemia, bleeding disorders or acute myeloid leukemia (AML).

MDS can affect children but is more common in people over the age of

60. Some research studies indicate the prevalence of MDS is increasing as life expectancies become longer. Caused by various gene mutations, the only cure for MDS is bone marrow transplant – a risky procedure that is often not a viable option, especially for older people.

Starczynowski and his colleagues wanted to identify a molecular target that affects MDS-related biological pathways. Their goal was to inhibit the molecule to see if that would suppress the duplication and expansion of MDS cells.

They worked from past studies that analyzed elevated gene expression in MDS cases and then conducted their own analyses of MDS and AML patient cells. The research team verified that an immune system enzyme called IRAK1 (Interleukin Receptor Associated Kinase-1) is highly over-expressed and hyper-activated in about 25 percent of MDS/AML cells.

The researchers then tested the effect of blocking IRAK1 on human MDS cells, on mouse models of human MDS and on normal human CD34+ blood cells. They used both direct genetic inhibition and a small-molecule inhibitor of IRAK1 (called IRAK-Inh) that was developed initially as prospective treatment for autoimmune disease and chronic inflammation.

Both genetic and pharmacologic inhibition of IRAK1 was effective at slowing the progression of human MDS cells and in mouse models of the disease. Inhibiting IRAK1 also had no effect on normal human CD34+ blood cells, showing it selectively targets MDS cells.

A possible shortcoming to IRAK-Inh treatment was discovered when researchers noticed it was not effective at overcoming a pro-cancer survival gene called BCL2. In some cell lines treated with IRAK-Inh, BCL2 genes became overexpressed in an effort to compensate for and work around the experimental treatment – a common occurrence in

certain cancer therapies.

Researchers responded by testing a collaborative treatment strategy, combining IRAK-Inh with an inhibitor of BCL2 called ABT-263. The combination treatment was effective at selectively targeting and killing MDS cells without harming normal blood cells.

Starczynowski cautioned that laboratory tests in mouse models and cell cultures do not necessarily translate into treatment for humans. Because IRAK1 is currently thought to be overexpressed in a subset of MDS patients, any prospective drugs targeting the enzyme would in theory benefit only that group.

Provided by Cincinnati Children's Hospital Medical Center

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