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Therapies for ALL and AML targeting MER receptor hold promise of more effect with less side-effect

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Two University of Colorado Cancer Center studies show that the protein receptor Mer is overexpressed in many leukemias, and that inhibition of this Mer receptor results in the death of leukemia cells – without affecting surrounding, healthy cells.

The first study, published today in the journal *Oncogene*, worked with acute myeloid leukemia (AML), for which current chemotherapies offer a cure rate of only about 55 percent.

"In about 2/3 of all AML patients and about 90 percent of adult AML patients, we found that the Mer receptor was upregulated. Mer receptor protein shouldn't exist in normal myeloid cells, but we found it abnormally expressed," says Doug Graham, MD, PhD, investigator at the CU Cancer Center and associate professor of pediatrics and immunology at the University of Colorado School of Medicine.

The Mer receptor sits within the cell membrane, and when it becomes activated the cell receives signals to grow and survive. Leukemia and perhaps many solid cancers have taken advantage of Mer's cell survival function to assist the cancer's rampant proliferation. When Graham and colleagues used shRNA to silence the production of Mer in leukemia cells, they showed decreased leukemia cell survival, increased sensitivity to existing chemotherapies and longer survival in mouse models of leukemia.

A second study, published this month in *Blood Cancer Journal*, shows similar results with acute lymphoblastic leukemia (ALL), the most common pediatric cancer.

"The ALL cure rate is already over 80 percent, but for patients who relapse, the prognosis is much less optimistic. We need targeted therapies to use as second-line treatments for the population for whom existing therapies aren't lasting, particularly in patients with relapsed T cell ALL," Graham says.

Second, he points out that a quarter of pediatric ALL patients who respond to existing chemotherapies do so at the price of significant long-term side-effects. "And so in addition to increased survival, the second goal of targeted therapies is decreased side-effects," Graham says.

Inhibition of the Mer protein receptor is promising on both accounts.

"Not only do B-cell and T-cell leukemia cells die when you knock down Mer receptor expression, but these cells are also much more sensitive to existing chemotherapies. By hitting Mer, we're making the chemotherapy more effective," Graham says.

In ALL and AML, Graham's studies show that making Mer inhibition means that less chemotherapy may have equal or stronger effect. Strong preliminary evidence shows that Mer may be the key to less toxic, more effective therapies for leukemia.

Provided by University of Colorado Denver