Disrupting tumor cell 'microenvironment' suggests a new way to treat a prevalent childhood leukemia

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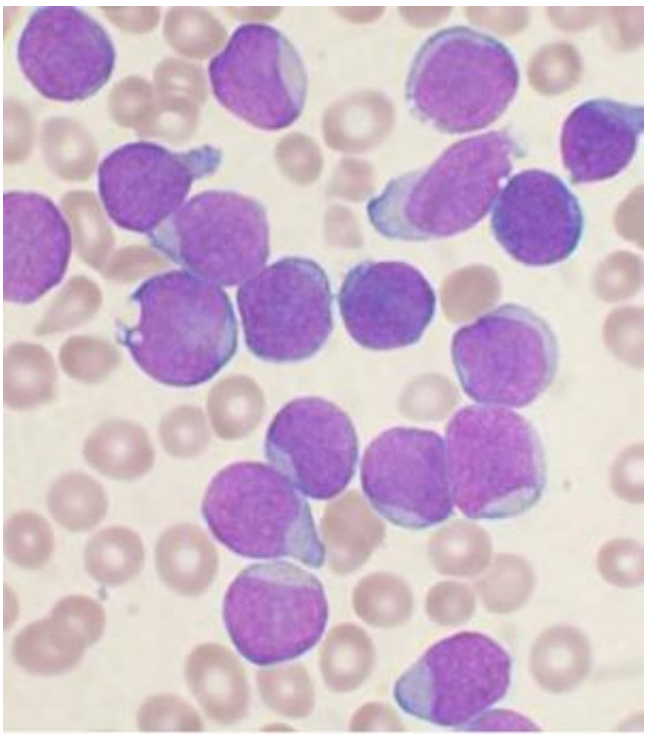

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

Researchers at NYU Langone Medical Center and its Laura and Isaac Perlmutter Cancer Center are reporting a potentially important discovery in the battle against one of the most devastating forms of leukemia that accounts for as many as one in five children with a particularly

aggressive form of the disease relapsing within a decade.

In a cover story set to appear in the journal *Cancer Cell* online June 8, researchers at NYU Langone and elsewhere report that they have successfully halted and reversed the growth of certain cancerous white blood cells at the center of T-cell acute lymphoblastic leukemia, or T-ALL, by stalling the action of a specific protein receptor found in abundance on the surface of T cells at the core of T-ALL.

In experiments in mice and human cells, researchers found that blocking CXCR4—a so-called homing receptor protein molecule that helps T cells mature and attracts blood cells to the bone marrow—halted disease progression in bone marrow and spleen tissue within two weeks. The experiments also left white blood cells cancer free for more than 30 weeks in live mice. Further, the research team found that in mice bred to develop T-ALL, depleting levels of the protein to which CXCR4 binds (CXCL12) also stalled T-ALL progression.

Researchers say their study results for the first time "clearly establish CXCR4 signaling as essential for T-cell acute lymphoblastic leukemia cell growth and disease progression."

"Our experiments showed that blocking CXCR4 decimated leukemia cells," says co-senior study investigator and NYU Langone cell biologist Susan Schwab, PhD.

Schwab, an assistant professor at NYU Langone and its Skirball Institute of Biomolecular Medicine, says similar laboratory test plans are underway for more potent CXCR4 antagonists, most likely in combination with established chemotherapy regimens. She notes that anti-CXCR4 drugs are already in preliminary testing for treating certain forms of myeloid leukemia, and have so far proven to be well-tolerated, but such treatments have not yet been tried for T-ALL.

Schwab says T-ALL is "a particularly devastating cancer" because there are not many treatment options.

One American survey, she points out, showed that only 23 percent of patients lived longer than five years after failing to sustain remission with standard chemotherapy drugs.

Co-senior study investigator and cancer biologist Iannis Aifantis, PhD, says the study offers the first evidence that "drugs targeting and disrupting leukemia cells' microenvironment—or what goes on around them—could prove effective against the disease."

Aifantis, the chair of the Department of Pathology at NYU Langone and a member of its Perlmutter Cancer Center, and an early career scientist at the Howard Hughes Medical Institute, says experiments in his laboratory had shown that leukemia-initiating cells concentrate in the bone marrow near CXCL12-producing blood vessels. This finding prompted a collaborative effort to investigate expression and function of CXCR4 because it binds to CXCL12, which in turn led to the researchers determining the vital role played by CXCR4-CXCL12 molecular signaling in disease growth.

Aifantis says more research needs to be done to decipher how CXCR4 is able to promote and sustain T-ALL.

As part of the new study, researchers deleted CXCL12 production specifically from bone marrow vasculature in leukemic mice. Disease progression in the bone marrow stalled within three weeks and tumors were smaller than in similar mice that retained CXCL12 production. Deletion of the CXCR4 gene led to sustained T-ALL remission within a month in similar mice, as well as movement of the cancerous blood cells away from the bone marrow. Subsequent transplant of millions of human T-ALL cells into normal mice that were then treated with an anti-

CXCR4 drug induced remission within two weeks, with diseased spleen and bone marrow tissue nearly returning to normal.

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