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Distinct niches in bone marrow nurture blood stem cells

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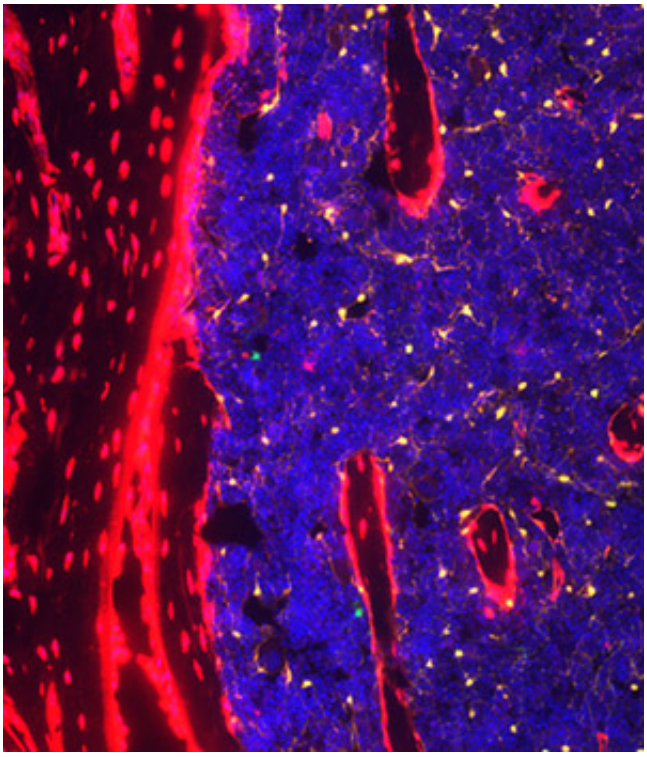

Distinct niches exist in bone marrow to nurture different types of blood stem cells, new research shows. In mice bone marrow, blood stem cells, highlighted in blue, are nurtured by support cells shown in red and yellow. Credit: Daniel Link, M.D.

In research that could one day improve the success of stem cell transplants and chemotherapy, scientists have found that distinct niches exist in bone marrow to nurture different types of blood stem cells.

Stem cells in the blood are the precursors to infection-fighting white blood cells and oxygen-carrying red blood cells.

The research, by a team at Washington University School of Medicine in St. Louis, is reported Feb. 24 in the advance online edition of *Nature*.

The new findings, in mice, suggest that it may be possible to therapeutically target support cells in a particular niche. On the one hand, a drug that nourishes support cells could encourage blood stem cells to establish themselves in the bone marrow, enabling patients who have had stem cell transplants to more quickly rebuild their immune systems.

On the other, tumor cells are known to hide in the bone marrow, and a drug that disrupts the niche environment may drive cancer cells into the bloodstream, where they are more vulnerable to the damaging effects of chemotherapy.

"Our results offer hope for targeting these niches to treat specific cancers or to improve the success of stem cell transplants," says senior author Daniel Link, MD, the Alan A. and Edith L. Wolff Professor of Medicine. "Already, we and others are leading clinical trials to evaluate whether it is possible to disrupt these niches in patients with leukemia or multiple myeloma."

Working in the mice, the researchers selectively deleted a critical gene, CXCL12, which is known to be important for keeping blood stem cells healthy. Rather than knock out the gene in all of the support cells in a niche, the researchers deleted the gene in specific types of support cells. This led to the discovery that each niche holds only certain blood stem cells that are nourished by a unique set of support cells.

"What we found was rather surprising," Link says. "There's not just one

niche for developing blood cells in the bone marrow. There's a distinct niche for stem cells, which have the ability to become any blood cell in the body, and a separate niche for infection-fighting blood cells that are destined to become T cells and B cells."

The findings provide a strong foundation for investigating whether disrupting these niches can improve the effectiveness of chemotherapy.

In a phase II pilot study led by Washington University medical oncologist Geoffrey Uy, MD, assistant professor of medicine, Link is evaluating whether the drug G-CSF can alter the stem cell niche in patients with acute lymphoblastic leukemia whose cancer has recurred or is resistant to treatment. The drug was approved by the Food and Drug Administration more than 20 years ago to stimulate production of white blood cells in patients undergoing chemotherapy, who often have weakened immune systems and are prone to infections.

But Uy and colleagues will evaluate the drug when it is given before chemotherapy. Patients enrolled in the trial at the Siteman Cancer Center will receive G-CSF for five days before chemotherapy, and the investigators will determine whether it can disrupt the protective environment of the bone marrow niche and make cancer cells more sensitive to chemotherapy.

While it's too early to know whether the treatment approach will be successful, Link's new research in mice is bolstered by a companion paper in the same issue of Nature. In that research, Sean Morrison, PhD, director of the Children's Medical Center Research Institute at the University of Texas Southwestern Medical Center in Dallas, used similar molecular methods to also discover distinct niches in the bone marrow for blood stem cells.

"There's a lot of interest right now in trying to understand these niches,"

Link adds. "Both of these studies add new information that will be important as we move forward. Next, we hope to understand how stem cell niches can be manipulated to help patients undergoing stem cell transplants."

More information: Greenbaum A, Hsu Y-MS, Day RB, Schuettpelz LG, Christopher MJ, Borgerding JN, Nagasawa T, Link DC. CXCL12 production by early mesenchymal progenitors is required for haemoatopoietic stem-cell maintenance. *Nature*. Advance online publication Feb. 24, 2013. DOI: 10.1038/nature11926

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