Duke research team identifies a potent growth factor for blood stem cells

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Duke Medicine researchers studying the interaction of blood stem cells and the niche where they reside have identified a protein that may be a long-sought growth factor for blood stem cells.

The protein is called pleiotrophin, and is produced by cells that line the blood vessels in bone marrow. In mouse studies conducted by the Duke researchers, the protein helps transplanted blood stem cells locate to the bone marrow, where they produce mature red and white blood cells in the body.

The finding, reported in the Oct. 18, 2012, issue of the journal *Cell Reports*, could lead to new treatments that speed recovery of healthy blood levels for patients receiving chemotherapy or undergoing bone marrow and cord blood transplants.

"Our hypothesis is that pleitrophin has the potential to promote blood stem cell growth in the manner that erythropoietin stimulates red blood cell precursors," said principal investigator John Chute, M.D., professor of Medicine, Pharmacology & Cancer Biology.

Many patients have benefitted from the discovery of erythropoietin (EPO), which stimulates the body to produce mature red blood cells. A synthetic form of EPO is commonly used to treat patients with anemia. Similarly, granulocyte colony stimulating factor (Neupogen), a growth factor for white blood cells, is used to remedy low white blood cell counts that often result from chemotherapy or radiation treatments for cancer.

"A principle objective in hematology for several decades is to identify a growth factor capable of promoting blood stem cells to grow without differentiating," Chute said.

Pleiotrophin may be one such growth factor. Pleiotrophin, which means "many forms," appears to make blood stem cells grow and promote production of all the mature blood lineages that are derived from the blood stem cell. Previously, Chute and his colleagues had shown that treatment with pleiotrophin promoted the expansion of mouse and human blood stems cells in cultures that were capable of engrafting in transplanted mice.

In the new research, lead researcher Heather Himburg, Ph.D., assistant professor of medicine, and Chute's research team showed that cells lining blood vessels in the bone marrow produce pleiotrophin, where it acts as a homing device to attract and retain stem cells. The researchers then demonstrated that genetically engineered mice missing the gene encoding pleiotrophin had decreased numbers of stem cells in their bone marrow, and had difficulty making new blood cells if depleted.

When the researchers treated normal mice with an anti-pleiotrophin antibody, it had the surprising effect of causing existing blood stem cells to be released from bone marrow and enter the blood stream. The finding was particularly exciting to the researchers, as the effect was similar to that observed when granulocyte-colony stimulating factor is used clinically to mobilize stem cells from a donor's bone marrow for use in blood stem cell transplants.

"The discoveries together suggest two possible therapeutic uses," said Chute. "Treatment with pleiotrophin may prove useful in helping patients more quickly regenerate their own blood forming cells after chemotherapy or bone marrow transplant. Second, anti-pleiotrophin antibodies may be useful in mobilizing stem cells to the peripheral blood."

The researchers are planning additional studies to understand how the homing system works and how pleiotrophin interacts with other growth factors to regulate blood stem cell function in the body. Given

that some prior studies have suggested that pleiotrophin can promote cancer cell growth, human safety studies will be crucial, Chute said.

Provided by Duke University Medical Center