Study identifies gene involved in blood stem cell replication, movement

April 9 2008

Researchers at the Joslin Diabetes Center have identified a gene that is responsible for the division and movement of marrow-derived, blood-forming stem cells, a finding that could have major implications for the future of bone marrow and blood cell transplantation.

Every year, some 45,000 patients undergo bone marrow or peripheral blood progenitor cell transplantation for the treatment of a variety of diseases, including leukemia, lymphoma, and immunodeficiency. Blood cell transplantation may also one day help people with diabetes better tolerate islet cell transplants without the need for prolonged use of powerful immunosuppressive drugs. In addition, transplantation of blood-forming stem cells, also called hematopoietic stem cells, may prove useful in halting the autoimmune process that causes type 1 diabetes.

The success of bone marrow and blood cell transplants depends on the ability of intravenously infused hematopoietic stem cells, which normally reside predominantly in the bone marrow, to accurately and efficiently migrate from the blood to the marrow of the transplant recipient and, once there, to repopulate their pool of mature blood cells.

In studying mice that lack the transcription factor early growth response gene (EGR-1), a team led by Amy Wagers, Ph.D., found that hematopoietic stem cells in the marrow of these animals divided about twice as often as stem cells in mice with the gene. Mice lacking EGR-1 also had higher numbers of such stem cells circulating in their blood.

The paper, published in the April issue of *Cell Stem Cell*, is the first to identify EGR-1 as a regulator of hematopoietic stem cell migration and proliferation. The transcription factor has already been identified as a tumor suppressor.

“The transcription factor EGR-1 is important in both of these processes,” said Wagers, Principal Investigator in the Joslin Section on Developmental and Stem Cell Biology, principal faculty member at the Harvard Stem Cell Institute and Assistant Professor of Pathology at Harvard Medical School. “This factor gives us a handle on the discovery of new pathways that regulate the movement of stem cells.”

The knowledge that EGR-1 suppression increases blood-forming stem cell production in the marrow and movement into the bloodstream suggests “a unique opportunity to target this pathway” to manipulate stem cell activity in the context of clinical bone marrow transplantation, the paper says.

“The process of cell migration is critical,” Wagers said. Migration of hematopoietic stem cells from the blood to the marrow is essential for effective transplantation, and the reverse process of migration from the marrow to the blood – an event called “mobilization” – is increasingly exploited for the collection of donor cells for transplant.

“By figuring out in future studies which genes this transcription factor is regulating we can find new ways, by targeting those genes, to enhance stem cell mobilization in people whose stem cells don’t mobilize well,” she said.

Bone marrow transplant patients are also vulnerable to infections in the period post-transplant when they may have insufficient numbers of blood cells. A mechanism to speed the recovery of normal levels of circulating blood cells, based on manipulations of EGR-1, would be

beneficial in this manner as well, the paper points out.

Source: Joslin Diabetes Center