Some blood-system stem cells reproduce more slowly than expected

December 5 2008

(PhysOrg.com) -- Investigators from Massachusetts General Hospital (MGH) have found a subpopulation of hematopoietic stem cells, the source of all blood and immune system cells, that reproduce much more slowly than previously anticipated. Use of these cells may improve the outcome of stem cell transplants – also called bone marrow transplants – for the treatment of leukemia and other marrow-based diseases. The report will appear in the journal *Nature Biotechnology* and is being released online to coincide with a similar study in the journal *Cell.*

"Hematopoietic stem cell transplantation saves many lives every day and is the most established therapeutic application of stem cells, but ironically we know very little about the cells that have made this clinical success possible," says Hanno Hock, MD, PhD, of the MGH Center for Regenerative Medicine, who led the study. "If we can improve our understanding of the biology of these cells, we should be able to offer our patients more therapeutic options."

It has been believed that the entire population of hematopoietic stem cells (HSCs) in the bone marrow reproduce at a rate of about 7 percent per day, with each cell dividing every two weeks. But previous investigations of stem cell proliferation appear to have missed the fact that some cells divide much less frequently. The MGH team developed a mouse model in which HSCs could be induced to express a green fluorescent label for a limited period of time. Tracking how long cells retained the label after its expression was halted indicated how long a cell remained in a resting phase between cell divisions.

While 80 percent of the labeled HSCs were observed to proliferate at the expected rate, 20 percent of cells reproduced much more slowly, dividing once every 100 days or longer. Another experiment found that a gene believed to keep HSCs in a resting state was not required to maintain the reduced rate of cell division in these slow-cycling HSCs, and a mathematical model of HSC proliferation only matched what was actually seen in the labeled mouse model if it assumed two populations of HSCs with differing rates of cell division.

To test whether the rate of proliferation changed the cells' ability to repopulate bone marrow, stem cell transplants were conducted using HSCs that had been labeled several months earlier and retained varying levels of the green marker – with higher label intensity signifying the slowly proliferating cells. The best results were achieved with cells maintaining the most label, which would signify the slow-cycling population, while cells in which the label was weakest were least able to repopulate the animals' marrow.

"Our results suggest that we understand a lot less about HSCs than we thought," Hock says. "If we can find more markers for these slow-cycling cells and identify them in human bone marrow, we may be able to make more of them and find additional clinical applications." An assistant professor of Medicine at Harvard Medical School, Hock is also associated with the MGH Cancer Center and the Harvard Stem Cell Institute.

Source: Massachusetts General Hospital