MicroRNA molecule increases number of blood stem cells, may help improve cancer treatment

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Investigators have identified a new mechanism that controls the number of hematopoietic stem cells - cells that give rise to all blood and immune system cells. In a report in the online Early Edition of *Proceedings of the National Academy of Sciences*, researchers from Massachusetts General Hospital (MGH) and the Harvard Stem Cell Institute identify a tiny RNA molecule that increases the number of these blood stem cells, an advance that may improve treatment of blood system cancers.

"This novel molecule raises blood stem cell numbers by suppressing the normal cell-death process," explains David Scadden, MD, director of the MGH Center for Regenerative Medicine and senior author of the report. "We've known that these non-coding RNAs can define what an immature cell will become, but none has previously been identified that can tell a blood system stem cell whether to live or die."

MicroRNAs - short strands of RNA not involved in the production of proteins - bind to and silence the expression of their target genes and play important roles in cellular development and differentiation, including the process by which hematopoietic stem cells (HSCs) mature into red or white blood cells. Since the process that controls the size of the HSC population is unknown, the researchers investigated whether microRNAs were involved. They found that loss of the enzyme Dicer, known to be essential to the generation of microRNAs, caused the death of HSCs, supporting the involvement of microRNAs in maintaining HSC

levels.

Futher investigation identified a cluster of microRNAs present at enhanced levels in HSCs and showed that one of them, miRNA-125a, increased numbers of HSCs by protecting them from the cell-death process that normally limits cellular populations. The protective effects of miRNA-125a were only seen at the stem-cell level and may involve suppression of the cell-death protein Bak1.

A related PNAS study from researchers at California Institute of Technology, also released online, found that elevated levels of a related molecule called miRNA-125b in HSCs could lead to an aggressive form of leukemia in mice. "These molecules modify cellular numbers in ways that can be both beneficial and detrimental, so it will be important to understand the differences," Scadden explains.

"We're now looking at ways to expand the stem cell population - to briefly turn on the anti-cell-death protection - to overcome limited levels of stem cells that can restrict the use of stem cell transplantation for patients with blood system failure and blood-cell cancers. Accomplishing that could make life-saving stem cell transplants available to more patients," he adds. Scadden is the Gerald and Darlene Jordan Professor of Medicine at Harvard Medical School and co-director of the Harvard Stem Cell Institute.

Provided by Massachusetts General Hospital