

Biologists discover microRNAs that control function of blood stem cells

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Hematopoietic stem cells provide the body with a constant supply of blood cells, including the red blood cells that deliver oxygen and the white blood cells that make up the immune system. Hematopoietic -- or blood -- stem cells must also make more copies of themselves to ensure that they are present in adequate numbers to provide blood throughout a person's lifetime, which means they need to strike a delicate balance between self-renewal and development into mature blood-cell lineages. Perturb that balance, and the result can be diseases such as leukemia and anemia.

One key to fighting these diseases is gaining an understanding of the genes and molecules that control the function of these stem cells. Biologists at the California Institute of Technology (Caltech) have taken a large step toward that end, with the discovery of a novel group of molecules that are found in high concentrations within hematopoietic stem cells and appear to regulate their production.

When the molecules, tiny snippets of RNA known as microRNAs (miRNAs), are experimentally elevated to higher levels in the [hematopoietic stem cells](#) of laboratory mice, they "either impede or accelerate the function of these cells," says David Baltimore, Robert Andrews Millikan Professor of Biology, recipient of the 1975 Nobel Prize in Physiology or Medicine, and principal investigator on the research.

A paper about the work was published July 26 in the early online edition

of the [Proceedings of the National Academy of Sciences](#) (PNAS).

Intriguingly, the researchers found that one particular miRNA, miR-125b, plays a striking dual role. When miR-125b was mildly elevated, it accelerated the production of mature blood cells by blood stem cells far better than any other miRNA. But when its expression was pushed to far higher levels, Baltimore says, "it led to a vicious cancer within 6 months." While the exact mechanism underlying this transformation event is presently unknown, it likely involves the inhibition by miR-125b of specific genes that normally suppress tumor formation.

"We were surprised to see that at high levels, miR-125b induced an aggressive myeloid leukemia in mice," says Caltech graduate student Aadel Chaudhuri, a coauthor on the paper. Myeloid leukemia results when normal blood cells—including [red blood cells](#), blood-clotting platelets, and [white blood cells](#)—are systematically replaced by abnormal white blood cells that continue to grow uncontrollably, ultimately leading to death if untreated.

"These studies were performed in mice," says Caltech postdoctoral scholar Ryan O'Connell, the lead author of the PNAS paper, "but we also analyzed human blood stem cells and found that the same miRNAs are similarly enriched."

In addition, the researchers found that the expression of that key miRNA enhances the engraftment of human blood stem cells when they are transferred into mouse hosts, "indicating that the expression and function of these miRNAs has been conserved during evolution," O'Connell says.

That means, Chaudhuri says, "it is possible that certain human leukemias could be treated by targeting these newly identified stem-cell microRNAs."

"These findings, when combined with a similar report by physician-scientist David Scadden of the Massachusetts General Hospital and the Harvard Stem Cell Institute, show that miRNAs are important molecules that control the function of blood stem cells," he says. "These observations have important implications for both the diagnosis and treatment of cancer and anemia, which arise from defective blood stem cells. Blood stem cell transplantations have become a common form of therapy to treat cancer, autoimmunity, and even certain types of infectious diseases, and the exploitation of miRNA expression levels in blood stem cells through therapeutic targeting could be used to augment this approach."

"These two studies add to the mounting evidence that miRNAs are critical controllers of the relative amounts of different types of blood cells made in the bone marrow of mice and people," Baltimore says. "In this work, we show that this is true for the stem cells, while earlier work from us and many others has shown that [miRNA](#) levels determine the concentrations of many types of mature blood cells. This knowledge offers the opportunity to therapeutically manipulate the levels of these blood cells," he says, "although targeting miRNAs therapeutically remains a great challenge to biotechnology."

Provided by California Institute of Technology

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