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Team finds new gene involved in blood-forming stem cells

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Research led by the University of Michigan Life Sciences Institute has identified a gene critical to controlling the body's ability to create blood cells and immune cells from blood-forming stem cells—known as hematopoietic stem cells.

The findings, scheduled for online publication in the *Journal of Clinical Investigation* April 13, provide new insights into the underlying mechanics of how the body creates and maintains a healthy blood supply and immune system, both in normal conditions and in situations of stress—like the body experiences following a bone marrow transplant.

Along with helping scientists better understand the body's basic processes, the discovery opens new lines of inquiry about the Ash1l gene's potential role in cancers known to involve other members of the same gene family, like leukemia, or those where Ash1l might be highly expressed or mutated.

"It's vital to understand how the basic, underlying mechanisms function in a healthy individual if we want to try to develop interventions for when things go wrong," said study senior author Ivan Maillard, an associate research professor at the Life Sciences Institute, where his lab is located, and an associate professor in the Division of Hematology-Oncology at the U-M Medical School.

"Leukemia is a cancer of the body's blood-forming tissues, so it's an obvious place that we plan to look at next. If we find that Ash1l plays a

role, then that would open up avenues to try to block or slow down its activity pharmacologically," he said.

Graduate students Morgan Jones and Jennifer Chase were the study's first authors.

Dysfunction of blood-forming stem cells is well known in illnesses like leukemia and bone marrow failure disorders. Blood-forming stem cells can also be destroyed by high doses of chemotherapy and radiation used to treat cancer. The replacement of these cells through bone marrow transplantation is the only widely established therapy involving stem cells in human patients.

But even in the absence of disease, blood cells require constant replacement—most blood cells last anywhere from a few days to a few months, depending on their type.

Over more than five years, Maillard and his collaborators identified a previously unknown but fundamental role played by the Ash1l gene in regulating the maintenance and self-renewal potential of these hematopoietic stem cells.

The Ash1l (Absent, small or homeotic 1-like) gene is part of a family of genes that includes MLL1 (Mixed Lineage Leukemia 1), a gene that is frequently mutated in patients who develop leukemia. The research found that both genes contribute to blood renewal; mild defects were seen in mice missing one or the other, but lacking both led to catastrophic deficiencies.

"We now have clear evidence that these genes cooperate to develop a healthy blood system," Maillard said.

His lab's investigation of the gene began at the prompting of co-author

Sally Camper, the James V. Neel Professor and Chair of the Department of Human Genetics in the U-M Medical School. Camper had been investigating Ash1l's role in endocrine and reproductive organs and saw clues that blood-forming tissues might also be affected.

The study found:

Ash1l-deficient mice had normal numbers of hematopoietic stem cells during early development, but a lack of stem cells in maturity—an indication the cells were not able to properly maintain themselves in the bone marrow.

Ash1l-deficient stem cells were unable to establish normal blood renewal after a bone marrow transplant. Moreover, Ash1l-deficient stem cells competed poorly with normal blood-forming stem cells in the bone marrow and could easily be dislodged.

Ash1l regulates the expression of multiple downstream "homeotic" genes, which help ensure the correct anatomical structure of a developing organism.

"This area of research really showcases the dynamic interplay between knowledge we can learn from human patients and discoveries undertaken in a laboratory setting," Maillard said.

After the U.S. dropped atomic bombs on Hiroshima and Nagasaki, doctors noticed that radiation patients weren't able to generate new white blood cells to fend off infections. Subsequent experiments on mice showed that bone marrow transplants from healthy animals into irradiated ones could renew their ability to make new blood cells. The technique was eventually developed for use in human patients, including those whose blood stem cells are killed off by cancer treatments. But work continues in the laboratory setting.

"By continuing to investigate the basic, underlying mechanisms—which builds on a history of research in fruit flies and in mice—we are helping to untangle the complex machinery of the blood renewal that may lay the foundation for new human treatments five, 10 or 20 years from now," Maillard said.

Provided by University of Michigan