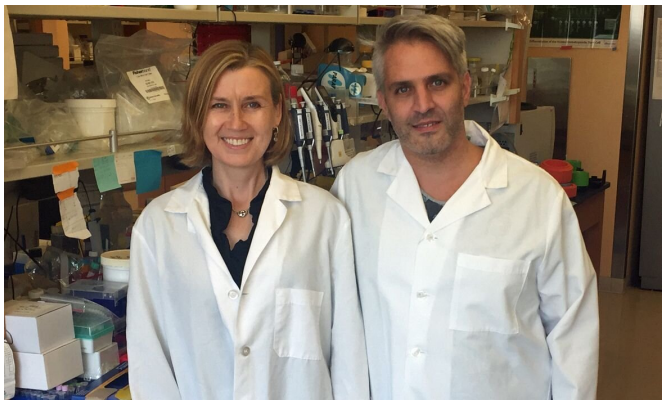
Researchers identify protein that governs human blood stem cell self-renewal

28 November 2019, by Mirabai Vogt-James



Dr. Hanna Mikkola and Vincenzo Calvanese. Credit: UCLA Broad Stem Cell Research Center

UCLA scientists have discovered a link between a protein and the ability of human blood stem cells to self-renew. In a study published today in the journal *Nature*, the team reports that activating the protein causes blood stem cells to self-renew at least twelvefold in laboratory conditions.

Multiplying blood stem cells in conditions outside the human body could greatly improve treatment options for blood cancers like leukemia and for many inherited blood diseases.

Dr. Hanna Mikkola, a member of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA and senior author of the study, has studied blood stem cells for more than 20 years.

"Although we've learned a lot about the biology of these cells over the years, one key challenge has remained: making human blood stem cells self-renew in the lab," she said. "We have to overcome this obstacle to move the field forward."

Blood stem cells, also known as hematopoietic stem cells, are found in the bone marrow, where they self-renew as well as differentiate to create all types of blood cells. Bone marrow transplants have been used for decades to treat people with some diseases of the blood or immune system. However, bone marrow transplants have significant limitations: Finding a compatible bone marrow donor is not always possible, the patient's immune system may reject the foreign cells, and the number of transplanted stem cells may not be enough to successfully treat the disease.

When blood stem cells are removed from the bone marrow and placed in laboratory dishes, they quickly lose their ability to self-renew, and they either die or differentiate into other blood cell types. Mikkola's goal, making blood stem cells self-renew in controlled laboratory conditions, would open up a host of new possibilities for treating many blood disorders—among them safer genetic engineering of patients' own blood stem cells. It could also enable scientists to produce blood stem cells from pluripotent stem cells, which have the potential to create any cell type in the body.

To uncover what makes blood stem cells self-renew in a lab, the researchers analyzed the genes that turn off as human blood stem cells lose their ability to self-renew, noting which genes turned off when blood stem cells differentiate into specific blood cells such as white or red cells. They then put the blood stem cells into laboratory dishes and observed which genes shut down. Using pluripotent stem cells, they made blood stem cell-like cells that lacked the ability to self-renew and monitored which genes were not activated.

They found that the expression of a gene called MLLT3 was closely correlated with blood stem cells' potential to self-renew and that the protein generated by the MLLT3 gene provides blood stem cells with the instructions necessary to maintain its ability to self-renew. It does this by working with other regulatory proteins to keep important parts of

the blood stem cell's machinery operational as the cells divide.

The researchers wondered if maintaining the level of the MLLT3 protein in blood stem cells in lab dishes would be sufficient to improve their self-renewing abilities. Using a viral vector—a specially modified virus that can carry genetic information to a cell's nucleus without causing a disease—the team inserted an active MLLT3 gene into blood stem cells and observed that functional blood stem cells were able to multiply in number at least twelvefold in lab dishes.

"If we think about the amount of blood stem cells needed to treat a patient, that's a significant number," said Mikkola, who is also a professor of molecular, cell and developmental biology in the UCLA College and a member of the UCLA Jonsson Comprehensive Cancer Center. "But we're not just focusing on quantity; we also need to ensure that the lab-created blood stem cells can continue to function properly by making all blood cell types when transplanted."

Other recent studies have identified small molecules—organic compounds that are often used to create pharmaceutical drugs—that help to multiply human blood stem cells in the laboratory. When Mikkola's team used the small molecules, they observed that blood stem cell self-renewal improved in general, but the cells could not maintain proper MLLT3 levels, and they also did not function as well when transplanted into mice.

"The previous discoveries with the small molecules are very important, and we're building on them," said Vincenzo Calvanese, a UCLA project scientist and the study's co-corresponding author. "Our method, which exposes blood stem cells to the small molecules and also inserts an active MLLT3 gene, created blood stem cells that integrated well into mouse bone marrow, efficiently produced all blood cell types and maintained their self-renewing ability."

Importantly, MLLT3 made the blood stem cells self-renew at a safe rate; they didn't acquire any dangerous characteristics such as multiplying too much or mutating and producing abnormal cells that could lead to leukemia.

The next steps for the researchers include determining what proteins and elements within blood stem cell DNA influence the on-off switch for MLLT3, and how this could be controlled using ingredients in the lab dishes. With that information, they could potentially find ways to switch MLLT3 on and off without the use of a viral vector, which would be safer for use in a clinical setting.

More information: Vincenzo Calvanese et al. MLLT3 governs human haematopoietic stem-cell self-renewal and engraftment, *Nature* (2019). DOI: 10.1038/s41586-019-1790-2

Provided by University of California, Los Angeles