

Researchers identify protein key to the development of blood stem cells

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Led by Dr. Hanna Mikkola, a member of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, UCLA scientists have discovered a protein that is integral to the self-replication of hematopoietic stem cells during human development.

The discovery lays the groundwork for researchers to generate hematopoietic [stem cells](#) in the lab that better mirror those that develop in their natural environment. This could in turn lead to improved therapies for blood-related diseases and cancers by enabling the creation of patient-specific blood stem cells for transplantation.

The findings are reported online ahead of print in the journal *Cell Stem Cell*.

Researchers have long been stymied in their efforts to make cell-based therapies for blood and immune diseases more broadly available, because of an inability to generate and expand human hematopoietic stem cells (HSCs) in lab cultures. They have sought to harness the promise of [pluripotent stem cells](#) (PSCs), which can transform into almost any cell in the human body, to overcome this roadblock. HSCs are the blood-forming cells that serve as the critical link between PSCs and fully differentiated cells of the blood system. The ability of HSCs to self-renew (replicate themselves) and differentiate to all blood cell types, is determined in part by the environment that the stem cell came from, called the niche.

In the five-year study, Mikkola, Dr. Sacha Prashad and Dr. Vincenzo Calvanese, members of Mikkola's lab and lead authors of the study, investigated a HSC surface protein called GPI-80. They found that it was produced by a specific subpopulation of human fetal hematopoietic cells that were the only group that could self-renew and differentiate into various blood cell types. They also found that this subpopulation of hematopoietic cells was the sole population able to permanently

integrate into and thrive within the blood system of a recipient mouse.

Mikkola and colleagues further discovered that GPI-80 identifies HSCs during multiple phases of human HSC development and migration. These include the early first trimester of fetal development when newly generated human hematopoietic stem cells can be found in the placenta, and the second trimester when HSCs are actively replicating in the fetal liver and the fetal bone marrow.

"We found that whatever HSC niche we investigated, we could use GPI-80 as the best determinant to find the stem cell as it was being generated or colonized different hematopoietic tissues," said Mikkola, associate professor of molecular, cell and development biology at UCLA and also a member of the Jonsson Comprehensive Cancer Center. "Moreover, loss of GPI-80 caused the stem cells to differentiate into mature [blood cells](#) rather than HSCs. This essentially tells us that GPI-80 must be present to make HSCs. We now have a very unique marker for investigating how human [hematopoietic cells](#) develop, migrate and function."

Mikkola's team is exploring different stages of human HSC development and PSC differentiation based on the GPI-80 marker, and comparing how [blood stem cells](#) are being generated in cultures (in vitro) and naturally (in vivo). This paves the way for scientists to redirect PSCs into patient-specific HSCs for transplantation into the patient without the need to find a suitable donor.

"Now that we can use GPI-80 as a marker to isolate the human [hematopoietic stem cell](#) at different stages of development, this can serve as a guide for identifying and overcoming the barriers to making [human](#) HSCs in vitro, which has never been done successfully," Mikkola said. "We can now better understand the missing molecular elements that in vitro-derived cells don't have,

which is critical to fulfilling the functional and safety criteria for transplantation to patients."

Provided by University of California, Los Angeles

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