Researchers find blood stem cells originate and are nurtured in the placenta

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Solving a long-standing biological mystery, UCLA stem cell researchers have discovered that blood stem cells, the cells that later differentiate into all the cells in the blood supply, originate and are nurtured in the placenta.

The discovery may allow researchers to mimic the specific embryonic microenvironment necessary for development of blood stem cells in cell culture and grow them for use in treating diseases like leukemia and aplastic anemia, said Dr. Hanna Mikkola, a researcher in the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research and senior author of the study.

“It was a big mystery, where these cells originated,” said Mikkola, an assistant professor of molecular, cell and developmental biology. “This is the first time we can really say definitively that blood stem cells are generated in the placenta. There’s no more speculation.”

The study is published March 6, 2008 in the journal *Cell Stem Cell*. Researchers in Mikkola’s lab are working now to replicate this work, done in mouse models, in humans.

“If we want to fully harness the potential of embryonic stem cells to treat disease, it’s critical for us to learn how to make tissue specific stem cells,” said Mikkola, who also is a researcher at UCLA’s Jonsson Comprehensive Cancer Center. “We can learn that by studying what happens during embryonic development.”

Scientists now can take embryonic stem cells, the cells that can become any tissue type in the body, and coax them into becoming all the cells in the blood supply, such as red and white blood cells and platelets. However, they can't make blood stem cells that self-new, or make more of themselves, and don't differentiate prematurely when transplanted into patients. The only way this currently can be achieved is by manipulating the cell's nuclear regulatory machinery with genes using retroviruses. To generate blood stem cells that are safe for use in patients, it is imperative that scientists learn how to generate self-renewing blood stem cells in a more natural way, by providing the correct developmental cues from the environment in which the cells develop.

Currently, patients with certain types of leukemia have one shot at a cure – a bone marrow transplant. However, there aren't nearly enough bone marrow donors to provide patients with perfect matches. Use of a less than perfect donor match carries a risk of graft vs. host disease, in which the immune cells from the donated marrow attack the body of the transplant patient. Cord blood contains blood stem cells, but not in large enough quantities to transplant an adult patient, Mikkola said.

If researchers could grow blood stem cells, those cells could be transplanted into these patients. The blood stem cells would then differentiate into a new, and healthy, blood supply. And with the recent success in creating induced pluripotent stem cells (iPS) from human skin cells, a patient's own skin cells could perhaps be used to create iPS cells. Those cells could then be transformed into blood stem cells, creating an immune-compatible source of blood supply that eliminates the risk of graft vs. host disease.

In her previous research, Mikkola and collaborators in Harvard and France had discovered that the placenta contained a large pool of blood stem cells, but it wasn't clear if they originated elsewhere and migrated

to the placenta to self-renew. Using a unique mouse model, a mouse embryo without a heartbeat, Mikkola and her team were able to find the blood stem cells at the site of their origin because there was no circulation of blood through the body.

“Using this model, we identified that the placenta has the potential to make hematopoietic (blood) stem cells with full differentiation ability to create all the major lineages of blood cells,” Mikkola said. “The placenta acts as a sort of kindergarten for these newly made blood stem cells, giving them the first education they need.”

It was previously known that blood stem cells could be found in the dorsal aorta, but there were so few located there that scientists reasoned it could not be the sole source of blood stem cells in the embryo. Mikkola’s discovery indicates that the blood stem cells are generated in the large arteries of the embryo and placenta, and then move to a specific site, or niche, where they expand and mature.

This recent study indicates that the first niche for expansion of blood stem cells is the placenta’s vascular labyrinth, where oxygen and nutrients are exchanged between the mother and the fetus. The findings show the placenta harbors two different microenvironments, one area where blood stem cells originate and another area, the labyrinth, that nurtures them, allowing them to expand in number. These niches serve different roles and could provide clues to researchers seeking to grow blood stem cells. Mikkola now is seeking to uncover the critical biological signals and cues during embryonic development that drive blood stem cell generation and expansion and keep the cells from differentiating prematurely.

“The labyrinth is a source of many growth factors and cytokines,” Mikkola said. “We just need to identify what those signaling molecules and cues are that are nurturing those cells when in the placenta.”

Mikkola is confident the study can be confirmed in humans.

“Everything we’re learning suggests we will find the same thing in the human placenta,” she said.

Source: University of California - Los Angeles