Study identifies essential molecule in formation of differentiated blood cells

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New research in the *Journal of Experimental Medicine* identifies a protein that controls the formation of different types of mature blood cells – a finding that could be important to developing new treatments for blood diseases and helping realize the potential of regenerative medicine.

Researchers from Cincinnati Children's Hospital Medical Center report their results in a study published online by the journal Oct. 7. The authors focus on a protein called RhoA, a GTPase that serves as a molecular switch in the cytoplasm of cells to control cell function.

The study shows RhoA is necessary for proper regulation of a cellular process called cytokinesis during the final stage of cell division in hematopoietic progenitor cells, which produce specific types of blood cells. Cytokinesis helps control the separation and grouping of genetic material as cells divide to decide their eventual fate.

Although the research was conducted in mouse models, the investigators said their findings will be important to the future study of various blood diseases, immune disorders and cancers. The data could also be useful for research into prospective strategies for regenerative medicine, in which pluripotent stem cells could be used to attempt the repair or regrowth of damaged tissues.

One example is human combined immunodeficiency, which has been linked to mutations in the RhoA pathway. The immune disorder makes people highly susceptible to infections their body cannot fight and its underlying cause remains unclear.

"We show that RhoA deficiency causes hematopoietic failure in all lines of blood cells and results in defective hematopoietic progenitor cells," said Yi Zheng, PhD, lead investigator and director of Experimental Hematology and Cancer Biology at Cincinnati Children's. "This is also important to understanding diseases like pancytopenia, in which people don't produce enough mature red and white blood cells and platelets. In regenerative medicine, it appears RhoA function would need to be artfully controlled to obtain functional blood cells."

Zheng and his colleagues conducted a series of experiments to confirm their data. One initial test involved subjecting hematopoietic stem cells in the mouse bone marrow to stressful conditions known to stimulate the production of blood cells. During this experiment, the researchers noted the involvement of active RhoA signaling during hematopoietic progenitor cell formation.

The researchers then tested the hematopoietic stem and progenitor cells of mice in which the RhoA gene was knocked out, causing depletion of RhoA protein in those cells. In one experiment, RhoA-deficient stem cells were transplanted into another group of mice to see how well they would function.

Following the transplant, researchers were surprised to learn that RhoA-deficient hematopoietic stem cells demonstrated long term engraftment, but they were unable to produce multi-potent hematopoietic progenitor cells or more differentiated blood cells. Instead, researchers observed an accumulation of progenitor cells with more than one nucleus (multi-nucleated cells) that failed to complete division and underwent programmed necrosis – a cell death mechanism.

In a final experiment, the researchers were able to restore the normal function of hematopoietic stem and progenitor cells by reconstituting RhoA in the cells. This resulted in the production of multi-lineage red and white blood cells.

Zheng and his colleagues have long studied disruptions in the RhoA GTPase pathway for their role in cancer formation, in which RhoA activity is

often elevated. The team has also developed prospective small molecular inhibitors to block abnormal pathway functions as possible new targeted treatments for various cancers.

Zheng said researchers are using data from their previous work along with the current study to look for new strategies to fight various blood or immune system disorders.

Provided by Cincinnati Children's Hospital Medical Center