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Loss of essential blood cell gene leads to anemia

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Researchers at Brigham and Women's Hospital (BWH) have discovered a new gene that regulates hemoglobin synthesis during red blood cell formation. The findings advance the biomedical community's understanding and treatment of human anemias and mitochondrial disorders.

The study will be published online on November 7, 2012 in *Nature*.

The researchers used an unbiased zebrafish genetic screen to clone mitochondrial ATPase inhibitory factor-1 gene, or Atpif1. The gene allows animals—zebrafish, mice and humans for instance—to efficiently make hemoglobin. Hemoglobin is the protein in red blood cells responsible for transporting oxygen in the blood.

The researchers found that loss of Atpif1 causes severe anemia. Moreover, the researchers uncovered a broader mechanistic role for Atpif1—regulating the enzymatic activity of ferrochelatase, or Fech. Fech is the terminal enzyme in heme (a component of hemoglobin) synthesis.

"Our study has established a unique functional link between Atpif1-regulated mitochondrial pH, redox potential, and [2Fe-2S] cluster binding to Fech in modulating its heme synthesis," said Dhvanit Shah, PhD, BWH Division of Hematology, Department of Medicine, first study author.

The researchers were also able to produce data on the human version of Atpif1, noting its functional importance for normal red blood cell differentiation, and noting that a deficiency may contribute to human diseases, such as congenital sideroblastic anemias and other diseases related to dysfunctional mitochondria (the energy powerhouses of cells).

"Discovering the novel mechanism of Atpif1 as a regulator of heme synthesis advances the understanding of mitochondrial heme homeostasis and red blood cell development," said Barry Paw, MD, PhD, BWH Division of Hematology, Department of Medicine, senior study author.

Shah and Paw continue to identify new genes responsible for hematopoietic stem cell development and red cell differentiation. Their identification of new genes will elucidate the new mechanisms regulating hematopoiesis—the formation of blood cell components. Their work not only provides greater insight into human congenital anemias, but also new opportunities for improved therapies.

Anemia, a condition in which your blood has a lower than normal number of red blood cells or hemoglobin levels, can affect people of all ages. Women of childbearing age and older adults are at higher risk. Babies and children are also at risk for anemia due to nutritional iron deficiency or lead poisoning.

Provided by Brigham and Women's Hospital