Scientists discover protein that allows safe recycling of iron from old red blood cells

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Humans survive by constantly recycling iron, a metal that is an essential component of red blood cells, but which is toxic outside of those cells. More than 90 percent of the iron in an adult human's 25 trillion life-sustaining red blood cells is recycled from worn-out cells.

Almost 50 years ago scientists first began hypothesizing that our bodies must have a special protein 'container' to safely transport heme—the form of iron found in living things – during the breakdown and recycling of old red blood cells and other types of heme metabolism. Now a team of scientists from the University of Maryland, Harvard Medical School, the National Institutes of Health and the University of Utah School of Medicine have identified this long-sought heme-iron transporter and shown that it is the same HRG1 protein that a common microscopic worm, *C. elegans*, uses to transport heme. In humans, the iron in heme is the component that allows hemoglobin in red blood cells to carry the oxygen needed for life.

The team's findings are based on studies in human, mouse, zebrafish and yeast systems and are published in the Feb. 5, issue of the journal Cell Metabolism.

"Our current work reveals that the long-sought heme transporter that permits humans to recycle over 5 million red blood cells per second in our spleen and liver, is the same HRG1 transporter protein that my students and I discovered in worms in 2008, and which we showed at that time is used by *C. elegans* to safely carry heme-iron that it obtains

from dirt into its intestine," says team leader and corresponding author Iqbal Hamza., a University of Maryland associate professor in the Department of Animal & Avian Sciences.

"Moreover, we show in this current study that mutations in the gene for HRG1 can be a causative agent for genetic disorders of iron metabolism in humans," he says.

First author Carine White, a UMD post-doctoral researcher and three other students from his lab joined Hamza in the research, along with researchers from Harvard, NIH and Utah.

This study's findings are the third major piece that Hamza and his Maryland lab have added to the puzzle of understanding how humans and other organisms safely move heme around in the body. In addition to their two studies showing the role of the HRG1, that Hamza showed in a 2011 Cell paper that in *C. elegans* there is a different, but related, protein called HRG3 that transports heme from the mother worm's intestine to her developing embryos.

According to Hamza, the HRG3-mediated pathway that worms use for transporting heme to developing oocytes also appears to be an excellent target for stopping the reproduction of hookworms and other parasites that feed on host red blood cell hemoglobin. Together these three findings could lead to new methods for treating two age-old scourges - parasitic worm infections, which affect more than a quarter of the world's population, and problems of iron metabolism and iron deficiency. The latter is the world's number one nutritional disorder. With the help of UMD's Office of Technology Commercialization and the university's Maryland Technology Enterprise Institute, Hamza has started a company, Rakta Therapeutics, Inc. that focuses on developing anti-parasitic drugs that specifically target the parasite's variation of HRG1 and HRG3 transporters.

Heme, Humans and Bloodless worms

In living organisms—ranging from humans to baker's yeast—iron enclosed in a heme cage is a critical molecule for health because it binds to oxygen and other gases needed for survival. However, because heme is toxic, scientists long ago started searching for the existence of proteins that could safely transport heme between cells and throughout the body.

However, identifying such proteins has been a very difficult task because organisms generate heme in a complicated eight-step process that is hard to control for in studies of heme transport pathways.

Hamza first started trying to uncover the secrets of heme transport in 2003. After briefly and unsuccessfully studying the question of heme carrying proteins in traditional bacteria and mice models, Hamza switched to a non-intuitive study subject, one that doesn't make heme, but needs it to survive, that doesn't even have blood, but shares a number of genes with humans - the *C. elegans* roundworm. *C. elegans* gets heme by eating bacteria in the soil where it lives. "*C. elegans* consumes heme and transports it into the intestine.

According to Hamza, *C. elegans* has had several other benefits for studying heme transport. Hamza's team had control of the amount of heme the worms were eating. With only one valve controlling the heme transport, the scientists knew exactly where heme was entering the worm's intestine, where, as in humans, it is absorbed.

Moreover, *C. elegans* is transparent, so that under the microscope researchers could see the movement of the heme ingested by a live animal.

More information: "HRG1 Is Essential for Heme Transport from the Phagolysosome of Macrophages during Erythrophagocytosis," *Cell*

Metabolism, Feb. 5, 2013.

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