Bloodless Worm Sheds Light on Human Blood, Iron Deficiency

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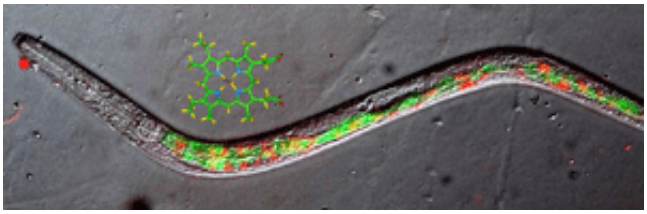

A C. elegans worm expressing the Green Fluorescent Protein and a fluorescent heme molecule (red) in the intestine. Credit: Jason Sinclair and Iqbal Hamza

Using a lowly bloodless worm, University of Maryland researchers have discovered an important clue to how iron carried in human blood is absorbed and transported into the body. The finding could lead to developing new ways to reduce iron deficiency, the world's number one nutritional disorder.

With C. elegans , a common microscopic worm that lives in dirt, Iqbal Hamza, assistant professor of animal and avian sciences, and his team identified previously unknown proteins that are key to transporting heme, the molecule that creates hemoglobin in blood and carries iron. It is a critical step in understanding how our bodies process iron. Their findings are published in the April 16 issue of *Nature* online.

"The structure of hemoglobin has been crystallized over and over," says Hamza, "but no one knows how the heme gets into the globin, or how

humans absorb iron, which is mostly in the form of heme.

"To understand the underlying issues of nutritional and genetic causes of iron deficiency, we are looking at the molecules and mechanisms involved in heme absorption. Once you understand transport of heme, you can more effectively deliver it to better absorb iron in the human intestine."

Heme and Blood

Heme is a critical molecule for health in all eukaryotes, organisms whose cells are organized into complex structures enclosed in membranes. Species of eukaryotes range from humans to baker's yeast. Heme makes blood red and binds to oxygen and other gases we need to survive.

Heme is created in the mitochondria, then moves through pathways that connect other cells, where it is synthesized to form blood. Heme on its own, however, is toxic. "We wanted to find out how heme gets carried between and within cells," said Hamza.

A Bloodless Worm

Eight steps are required to generate heme, making it a difficult process to control in the study of heme transport pathways, as Hamza learned when he first studied the question in bacteria and mice.

So Hamza did the non-intuitive thing. He chose a test subject 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, a simple nematode.

"We tried to understand how blood is formed in an animal that doesn't

have blood, that doesn't turn red, but has globin," Hamza said.

C. elegans gets heme by eating bacteria in the soil where it lives. "C. elegans consumes heme and transports it into the intestine. So now you have a master valve to control how much heme the animal sees and digests via its food," Hamza explains.

C. elegans has several other benefits for studying heme transport. Hamza's team could control 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.

And C. elegans is transparent, so that under the microscope researchers could see the movement of the heme ingested by the worm.

Genes and Iron Deficiency

The study revealed several findings that could lead to new treatment for iron deficiency. One was the discovery that genes are involved in heme transport. Hamza's group found that HRG-1 genes, which are common to humans and C. elegans , were important regulators of heme transport in the worm.

To test their findings in an animal that makes blood, Hamza's team removed the HRG-1 gene in zebrafish. The fish developed bone and brain defects, much like birth defects. The gene removal also resulted in a severe form of anemia usually caused by iron deficiencies.

When they substituted the zebrafish gene with the worm HRG-1 gene, the mutant fish returned to normal, indicating that the fish and worm genes are interchangeable, irrespective of the animal's ability to make blood.

They also found that too little or too much heme can kill C. elegans , a result that could help researchers find ways to treat people who suffer from iron deficiency caused by parasitic worms.

"More than two billion people are infected with parasites," says Hamza. "Hookworms eat a huge amount of hemoglobin and heme in their hosts. If we can simultaneously understand heme transport pathways in humans and worms, we can exploit heme transport genes to deliver drugs disguised as heme to selectively kill parasites but not harm the host."

Link: *Nature* paper www.nature.com/nature/journal/ … abs/nature06934.html

Source: University of Maryland