Worm study yields insights on humans, parasites and iron deficiency

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Studying the bloodless worm, *C. elegans* (pictured here), University of Maryland researchers have discovered a protein involved in the process by which humans, and other organisms safely move iron around in the body. The findings, published in the journal Cell, could lead to new methods for treating age-old scourges - parasitic worm infections, which affect more than a quarter of the world's population, and iron deficiency, the world's number one nutritional disorder. In this image, the *C. elegans* worm is expressing a green fluorescent protein and a fluorescent heme molecule (red) in the intestine. Credit: Credit: Jason Sinclair and Iqbal Hamza, University of Maryland

Using a tiny bloodless worm, University of Maryland Associate Professor Iqbal Hamza and his team have discovered a large piece in the puzzle of how humans, and other organisms safely move iron around in the body. The findings, published in the journal *Cell*, could lead to new methods for treating age-old scourges - parasitic worm infections, which affect more than a quarter of the world's population, and iron deficiency, the world's number one nutritional disorder.

Using *C. elegans*, a common microscopic worm that lives in dirt, Hamza and his team have identified a protein, called HRG-3 that transports heme from the mother's intestine to her developing embryos. This finding builds on a breakthrough Hamza's team made three years ago, when he and colleagues discovered HRG-1, a protein common to humans, which transports heme from the environment into the intestine of *C. elegans*.

Iron is an absolute requirement for humans and most other forms of life, but, because it is a free radical 'instigator,' it can also be toxic. To protect themselves, organisms surround iron with protein escorts to allow it to be safely moved within the body. The most important class of iron-containing compound is heme in hemoglobin, the most familiar iron-binding protein which carries oxygen and makes blood red.

"We've known the structure of hemoglobin for a really long time," said Hamza, "but we haven't been able to figure out how the heme gets into the globin, or exactly how humans and other living organisms move heme, which like iron is toxic, around and between cells."

Hamza first started trying to uncover the secrets of heme transport in 2003. He and his team were studying the molecules and mechanisms involved in heme absorption in the intestine of *C. elegans* when, in 2008, they discovered that the protein HRG-1 escorts heme into the worm's gut, the first step of the intercellular journey.

"Now, in this current study we've looked at the next step in the transport process, which is how the worm moves heme from the intestine to other parts of its body" he said.

Hamza explained that for this next step they chose to study transport of heme between the mother's intestine and developing embryos because studies in mammals had implied the existence of a pathway for ferrying and depositing mother's heme into her embryos, but no such route had been identified.

In *C. elegans*, it was easier to manipulate experimental conditions to clearly see the life and growth impacting effects of the presence or absence of heme while simultaneously looking at two separate organisms – the mother and her embryos all residing within a fully transparent living animal.

"What we've found in our current study is that this protein, which we named HRG-3, takes heme from the worm intestine to the embryos," he said. "We believe this protein is also involved in transport of heme from the worm intestine to the other parts of a worms' body such as its brain, skin and muscle."

For organisms that can make their own heme, from bacteria to humans, it takes eight steps. For decades this complicated synthesis pathway acted as an obstacle that stymied all attempts to study heme transport using the usual lab suspects like rats or mice or yeast.

Early in his research of heme transport, Hamza, tried to use mice and yeast, but encountered the same seemingly intractable obstacle. But then he got the inspiration to try a non-intuitive approach and decided to test an organism that doesn't make heme, but needs it to survive. One that doesn't even have blood, but shares a number of genes with humans - the roundworm *C. elegans*, a microscopic soil nematode.

"We are studying 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. It 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 explained.

C. elegans has several other benefits for studying heme transport. Hamza's team can control the amount of heme the worms eat. With only one 'valve' controlling the heme transport, the scientists knew exactly where heme was entering the worm's body. In humans, it is synthesized in trillions of body cells.

Hamza explained that *C. elegans* have another distinct advantage as study subject, they are transparent. By adding a fluorescent marker to heme that the worms will ingest, researchers can actually see the heme that a worm takes in as it moves within the worm's body.

Parasitic worms including hookworms, whipworms and threadworms are similar to *C. elegans* in that they get heme from external sources. Thus both, *C. elegans* and parasitic worms, are likely to be dependent on the same heme transport pathways for growth and reproduction. In their study in *Cell*, Hamza and his colleagues say their new findings indicate that a prime target for new treatments against parasitic worms is the HRG-3-mediated pathway by which heme is transported to developing eggs.

"More than two billion people are infected with parasitic worms," says Hamza. "Hookworms, alone, infect more than a billion people. These worms eat a huge amount of hemoglobin and heme in their hosts. By simultaneously understanding 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."

Hamza, also said he believes that filling in pieces of the heme transport puzzle is beginning to reveal the possibility of new therapeutic approaches to treating iron deficiency, the world's number one nutritional disorder.

"Perhaps, given the importance of heme in many different metabolic processes in the body, heme transport research may even yield new insights into other health issues," he said.

Hamza has co-founded a new company called HemeCentric, Inc. to develop anti-parasite drugs and heme-based iron supplements based upon discoveries in heme biology and iron regulation. HemeCentric recently won the Warren Citrin Social Impact Award during the 2011 University of Maryland Business Plan Competition.

More information: "An Intercellular Heme-Trafficking Protein Delivers Maternal Heme to the Embryo during Development in C. elegans," Cell, May 27, 2011.

Provided by University of Maryland

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