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Structure of iron regulatory protein-RNA complex solved

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The surprising structure and properties of a protein responsible for regulating the transport, storage and use of iron -- as it binds its target RNA -- are described by researchers from the University of Illinois at Chicago in the Dec. 22 issue of Science.

Iron is an essential nutrient, and defects in uptake and metabolism that result in either deficiencies or overload of iron cause a variety of diseases and disorders, including heart disease, arthritis and cancer.

The iron regulating protein, called IRP1, has two structural forms, each with important functions within the cell.

When serving as one of two regulators of cellular iron metabolism through its control of gene expression, the tightly coiled IRP1 opens up to expose sites that bind messenger RNA at sites on the RNA called iron responsive elements, or IREs, that are common in genes involved in iron metabolism.

In its alternate form, IRP1 binds a cluster of iron and sulfur atoms to act as an important metabolic enzyme called aconitase. The assembly and disassembly of the iron/sulfur cluster in the aconitase form appears to be an effective mechanism for regulating IRP1 activity.

"We found that when IRP1 releases the iron/sulfur cluster and opens up to bind RNA, it undergoes an extraordinary, unexpected rearrangement," said William Walden, professor of microbiology and immunology at

UIC and lead author of the study.

"This is the crucial step in understanding the specialized cellular processes that have evolved to maintain internal iron concentrations at the appropriate safe and useful levels and is important to the future design of therapeutic targets," Walden said.

IRP1 is a very large protein, composed of about 900 amino acids arranged into four major domains.

"We expected that IRP1 would open up the two major domains facing each other along a hinge, rather like a clam shell, to accommodate the RNA binding," Walden said. "What we didn't expect was that that opening up would also involve extensive movement within the domains."

The researchers also found two widely separated contact sites between IRP1 and the iron responsive element, said Karl Volz, associate professor in of microbiology and immunology at UIC and principle investigator of the study.

"This is one of the highest affinity bindings we have ever seen. The effect of binding a single iron responsive element, through interactions at two separate binding sites, essentially eliminates the possibility of non-specific binding," Volz said.

According to coauthor Elizabeth Theil, senior scientist at the Children's Hospital Oakland Research Institute in Oakland, Calif., just as drugs targeted to the three-dimensional protein structure emerged in the last century, "knowing how the iron response element RNA is folded in the IRP1 complex is a gift to drug design targeted to 3-D RNA structure -- a developing goal in this century."

The researchers believe the details of the IRP1:IRE interaction are likely

also to apply to the other important iron regulatory molecule, IRP2, they wrote in their conclusion. "What remains to be determined is the evolutionary origin and selective advantage of such dramatic conformational plasticity and dual functionality as found in IRP1."

Source: University of Illinois at Chicago