Structural Implications into Frataxin's Role in Heme and Iron-Sulfur Cluster Biosynthesis

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Frataxin, a nuclear encoded protein that is targeted to the mitochondrial matrix, has recently been implicated to participate within the cellular heme and iron-sulfur cluster bioassembly pathways by acting as an iron chaperone. Humans with a frataxin deficiency have the neurodegenerative disorder Friedreich's ataxia, which is characterized by a deficiency in the ability to produce these iron cofactors, coupled with elevation in mitochondrial iron levels and the formation of iron deposits. In vitro studies confirm frataxin binds iron and activity assays indicate iron loaded frataxin mediates heme and iron sulfur cluster synthesis by delivering metal to ferrochelatase and ISU apparatus enzymes, respectively. Overall, these results correlate well with published *in vivo* studies that suggest frataxin plays a direct role in heme and iron-sulfur cluster biosynthesis.

Our laboratory has taken a structural approach to help elucidate frataxin's role within these iron cofactor biosynthetic pathways. The solution structure of full-length "mature" yeast frataxin has been solved, providing the framework to help understand how the protein binds iron. X-ray absorption spectroscopic studies, comparing monomeric iron loaded yeast and human frataxin, have provided insight into the redox ability of bound metal and a structural understanding of how frataxin binds iron. Solution titration studies have been used to measure the iron binding affinity of yeast frataxin and to identify specific frataxin amino acids that act as ligands to the metal. In vivo and in vitro mutational analyses have been used to test the role of these residues within metal binding and metal delivery. Finally, solution studies on both the yeast and human proteins have been used to map he intermolecular interface between frataxin and protein binding partners. Our results have helped us develop a model for how frataxin delivers ferrous iron during cellular heme and iron-sulfur cluster bioassembly.