Iron Binding Studies Of Yeast Frataxin

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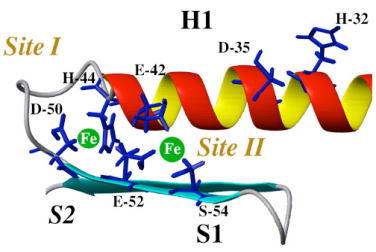
Iron is an essential nutrient for all cells, and is required in many sub-cellular locations. The organelle with the greatest iron requirement is mitochondrion, where it is required for the assembly of the iron-sulfur centers and heme biosynthesis. Frataxin, a nuclear encoded mitochondrial protein plays a major role in mitochondrial iron homeostasis. Frataxin is the only known iron chaperone. Deficiency of Frataxin in humans leads to Friedreich's ataxia (the most prevalent form of the hereditary ataxias), a spinocerebellar degeneration disorder that causes progressive damage to the nervous system. The phenotype of this disorder is iron accumulation in mitochondria, seen predominantly in nerve and muscle cells (leading to oxidative stress) coupled with breakdown in heme and iron sulfur cluster assembly.

Our lab is the first to solve the solution structure of the full-length eukaryotic apo-frataxin (Yfh1). We have shown monomeric Yfh1 binds iron and have identified what we believe are the iron binding residues on the protein. Based on our experimental results, we developed a model for how Yfh1 binds iron. To examine the role of specific residues in iron binding, Yfh1 mutants with substitutions at our iron binding-residues were prepared and characterized for metal binding. Physiological relevance of our results was tested by *in vivo* studies of our mutants in *S.cerevisiae.In vitro* and *in vivo* results support our "two- site" binding model and indicate that the residues we identified are the iron binding residues of frataxin.



Yfh1

Left: Two-Site Iron Iron Binding Model

Right: Residues Perturbed By Iron