Characterization of Metal Binding Properties of the Mitochondrial Iron Chaperone Frataxin

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Iron is a critical component in heme and iron-sulfur clusters. Proteins utilize both hemes and iron sulfur clusters to accomplish processes like O_2 delivery and ATP production. The protein "Frataxin" has been identified as assisting in heme and Fe-S cluster biosynthesis by acting as a mitochondrial iron chaperone in the early stages of both pathways. Deletion of the frataxin gene results in mitochondrial iron accumulation, which eventually leads to cell death as a result of oxidative stress. Patients with a frataxin deficiency develop the neurodegenerative disorder Friedreich's ataxia.

One goal of the Stemmler laboratory is to characterize the iron binding properties of frataxin. In doing so, we hope to provide a better understanding of how frataxin performs as an iron chaperone. We recently solved the full length solution structure of yeast frataxin (from *Saccharomyces cerevisiae),* and identified important iron binding residues in both the human and yeast proteins, using NMR spectroscopy. Using a variety of techniques (NMR, ITC, XAS), we have characterized the affinity and structure of iron bound to monomeric yeast and human frataxin. Our data indicate that monomeric yeast frataxin binds two iron atoms at micromolar binding affinities, and this iron is bound within an oxygen/nitrogen only based ligand geometry. Monomeric human frataxin binds iron with similar affinities and in a similar iron coordination geometry. Both results are consistent with our NMR studies. In addition, we have probed the redox nature of metal bound to monomeric frataxin and have shown the protein can partially stabilize iron in the reduced (ferrous) form when exposed to molecular oxygen. These results have direct implications into frataxin's role as a cellular iron chaperone.