Frataxin deficiency alters the heme pathway and a homolog of a yeast metallochaperone in mammalian cells

Robert A. Schoenfeld[1+], Elenora Napoli[1+], Alice Wong, Shan Zhan[1], Dexter Morin, Alan Buckpitt, Franco Taroni[2], Bo Lonnerdal, Michael Ristow[3], Helene Puccio[4] and Gino A. Cortopassi[1*]

[1] Department of Molecular Biosciences, University of California, Davis
[2] Division of Bichemistry and Genetics, Instituto Nazionale Neurologico ,Carlo Besta,' Via Celoria 11, Milan, Italy
[3] Deutsches Institut fur Emahrungsforschung, Potsdam, Germany
[4] Institut de Genetique et de Biologie Moleculaire et Cellulaire, CNRS/INSERM/Universite Louis Pasteur, Strasbourg, France

Deficiency of the frataxin mRNA alters the human and mouse transcriptome, triggering neuro- and cardiodegeneration, and causing Friedreich's ataxia. We microarrayed frataxin-deficient hearts, cardiocytes and livers of mice and observed mitochondrial localization of transcriptional changes, a transcript down-regulation to up-regulation ratio of 2:1 and uniform repression of OXPHOS transcripts. Combining all microarray data from mouse and human cells, the most consistently decreased transcripts were in mitochondrial coproporphyrinogen oxidase of the heme pathway (CPO), and MTCP1, a homolog of yeast COX23, which is thought to function as a mitochondrial metallochaperone. Consistent with microarray, we observed in human FRDA cells: 1) a decrease in heme flux; 2) a defect of heme insertion into cytochrome c; 3) significant correlation of heme insertion with frataxin concentration, and 4) increased protoporphyrin IX and heme concentrations in mutants. The mean Zn-chelatase activity of mutants was elevated, while Fe-chelatase activity was unchanged, suggesting an altered metal specificity of ferrochelatase, which might influence the insertion of heme into hemoproteins. Consistent with the proposed function of the MTCP1 homolog COX23, cytochrome oxidase activity decreased in mutants, with no decrease in concentration of subunit I or II, consistent with decreased metallation or assembly. We note that decreased metal delivery or assembly of cytochrome oxidase could cause decreased utilization of the aa and aa3 heme of cytochrome oxidase. Thus, frataxin appears to facilitate the insertion of heme into hemoproteins, perhaps through its alteration of the metal-specificity of ferrochelatase, or through co-regulation of MTCP1, or both. Since frataxin has previously been demonstrated to have multiple effects on FeS cluster biosynthesis and stability, one interesting question is whether frataxin primarily affects FeS, from which the heme alterations follow, or whether frataxin primarily affects the heme pathway, from which the FeS alterations follow. Since ataxic symptoms occur in other diseases of heme deficiency, the heme defect observed in FRDA cells could be primary to the pathophysiologic process.