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Commentary

Friedreich's ataxia is a mitochondrial disorder

*Jerry Kaplan**

Department of Pathology, School of Medicine, University of Utah, Salt Lake City, UT 84132

Friedreich's ataxia (FRDA) is the most common of the early-onset inherited ataxias and accounts for approximately half of the cases of hereditary ataxia reported from Europe and the United States (1). FRDA is transmitted as an autosomal recessive trait, with a prevalence of about 2 per 100,000. Disease symptoms typically appear between the ages of 8 and 15 years, but some patients develop symptoms earlier in childhood. In rare instances, disease manifestations occur as late as the third or fourth decade (2, 3). Gait ataxia is the most common presenting symptom. Dysarthria, areflexia, pyramidal weakness of the legs, extensor plantar responses, distal loss of joint position, and vibration sense are not found in all patients at the time of presentation but are eventually universal. FRDA is usually defined as a neurological disorder, but most patients die from cardiomyopathy. The gene responsible for FRDA was identified by positional cloning and encodes a relatively small protein of 210 amino acids (4). The gene itself is small, encompassing only five exons. The most common mutation is an expansion of a GAA trinucleotide repeat within the first intron. Although normal individuals may have up to 27 GAA repeats, affected individuals have greater than 100 repeats, and repeat sizes of greater than 1,000 have been identified. Affected individuals synthesize a normal sized protein, termed Frataxin, but the expanded repeat decreases the amount of protein synthesized (5). During transcription, the expanded repeat induces a triple helical structure, which lowers the rate of transcription (6). The larger the repeat, the greater the effect on transcript and protein levels. Compound heterozygotes have been identified with a triplet expansion in one allele and either a nonsense mutation, missense point mutation, or initiation codon mutation in the other allele (7). To date, no patient has been identified with homozygosity for a null mutation, and it is predicted that a homozygous null would prove lethal in early embryonic life.

The sequence of Frataxin yielded little insight into the function of the protein, but studies of the yeast homologue of Frataxin (*YFH1*) led to a hypothesis regarding the function of Frataxin and the pathophysiology of FRDA. *YFH1* was found to encode a mitochondrial protein involved in iron metabolism (8, 9). Reduced levels of protein led to an increase in mitochondrial iron concentration, resulting in decreased mitochondrial respiration. The concept that FRDA is a mitochondrial disorder is strongly supported by the report of Lodi *et al.* (10) presented in this issue of the *Proceedings*.

Deletion of the *YFH1* gene in the budding yeast *Saccharomyces cerevisiae* resulted in a loss of mitochondrial respiration and the formation of petite strains (8, 11–13). Further studies demonstrated that the loss of respiration followed the accumulation of iron in mitochondria (9). These observations led to the hypothesis that the accumulated iron reacting with H_2O_2, a major byproduct of oxidative respiration, generated hydroxyl radicals that would damage lipids, proteins, and the mitochondrial genome. The defect in respiratory activity is associated with increased mitochondrial chromosomal mutations. Reduction in iron accumulation, either by limiting media iron or by deleting genes required for high-affinity iron transport, was found to maintain respiratory activity in Δ*yfh1* strains, whereas increased concentrations of H_2O_2 or iron enhanced damage (8, 9, 12). Yfh1p was shown to regulate mitochondrial iron export, establishing the presence of a dynamic mitochondrial iron cycle (9). Mitochondria both import and export iron. Studies have shown that mitochondria can export not only heme iron but also iron in the form of iron-sulfur clusters (14).

Studies in yeast have led to a plausible model for the pathophysiology of FRDA. The Frataxin gene also encodes a mitochondrial protein (5, 8, 15), and Frataxin c-DNA, with minor modifications of the leader sequence, can complement Δ*yfh1* yeast strains (11). These results indicate that the human and yeast genes are orthologues—homologous genes with similar functions. Cardiac biopsies on two patients with FRDA revealed deficits in iron-sulfur enzymes, but the activities of tricarboxylic enzymes were normal (16). The study of Lodi *et al.* establishes that FRDA is a mitochondrial disorder (10). These authors used ^{31}P-NMR to quantify phosphate and ATP levels in skeletal muscles from patients with FRDA. They found that at rest, skeletal muscle phosphate levels were higher than normal in patients with FRDA, a finding also observed in other neuromuscular defects. What is unique is that on exercise FRDA patients showed a profound decrease in their ability to increase ATP levels by oxidative metabolism. Decreased oxidative metabolism could not be explained by muscle atrophy resulting from inactivity, because impaired oxidative metabolism was not seen in patients with compromised neuromuscular activity from other causes. Most compelling was the observation that decreased oxidative activity was directly correlated with the size of the GAA repeat. This result indicates a causal relationship between Frataxin and the mitochondrial deficit.

Lodi *et al.* point out that skeletal muscle deficits are not clinically apparent in patients with FRDA (10), and it is not clear why the disease phenotype is so prominent in the nervous system and the heart. These tissues have the greatest expression of Frataxin and might be expected to show the greatest phenotype, but if Frataxin affects mitochondrial function, why are other mitochondria-rich tissues, such as skeletal muscle, not clinically affected? One explanation, suggested by Lodi *et al.*, is that because of their disorder FRDA patients cannot exercise to the point at which a skeletal muscle defect is apparent. A second potential answer has been provided by a recent publication in the *Proceedings* (17). Cardiac and skeletal muscles show vastly different responses to deficits in ATP generation. Deletion of the murine mitochondrial ADP/ATP transporter gene results in decreased ATP generation and increased H_2O_2 production in both cardiac and skeletal muscle (13). Cardiac tissue, however, suffers a more profound functional deficit than skeletal muscle. Esposito *et al.* (17) demonstrated that skeletal muscle can increase antioxidant defenses to a greater level than cardiac muscle, thus rendering the latter more susceptible to oxidant damage. A third answer is

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*To whom reprint requests should be addressed. E-mail: Kaplan@BioScience.Biology.Utah.Edu.

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that skeletal muscle derives a significant amount of energy from glycolysis, whereas cardiac myocytes derive most of their ATP from the oxidation of free fatty acids. Mitochondrial defects would preferentially be seen in tissues that are most reliant on respiratory oxidation.

The study of Lodi *et al.* provides the proof that FRDA is a mitochondrial disorder, but the mechanisms underlying the mitochondrial deficit remain to be clarified. The yeast studies implicate excessive iron accumulation in mitochondria. Two studies have indicated that mitochondria obtained from cultured FRDA fibroblasts have more iron than mitochondria from control fibroblasts (18, 19). Waldvogel *et al.* (20) inferred a higher-than-normal concentration of iron in the dentate nucleus of FRDA patients on the basis of analysis of magnetic resonance imaging. Finally, tissue obtained at autopsy (21) and cardiac biopsies obtained from living patients with FRDA (unpublished work) show unique iron deposits in cardiac myocytes, although it has not been established that the deposits are localized to mitochondria.

Mitochondria now become the focus of potential therapeutic interventions in FRDA, and ^{31}P-NMR of skeletal muscle tissue could serve as an objective measure of potential treatment efficacy. The Frataxin gene was identified only 4 years ago, and now we have a robust hypothesis about the pathophysiology of FRDA and an objective assay for the efficacy of therapeutic interventions.

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