Friedreich ataxia, the most common type of inherited ataxia, is itself caused in most cases by a large expansion of an intronic GAA repeat, resulting in decreased expression of the target frataxin gene. The autosomal recessive inheritance of the disease gives this triplet repeat mutation some unique features of natural history and evolution. Frataxin is a mitochondrial protein that has homologues in yeast and even in gram-negative bacteria. Yeast organisms deficient in the frataxin homologue accumulate iron in mitochondria and show increased sensitivity to oxidative stress. This suggests that Friedreich ataxia is caused by mitochondrial dysfunction and free radical toxicity.

Friedreich ataxia (FRDA) is the most common of the hereditary ataxias. Its prevalence is around $2 \times 10^{-5}$ in almost all studied populations, with local clusters caused by a founder effect, as in Rimouski, Quebec, or Kathikas-Arodhes, Cyprus.

The disease was first described in 1863 by Nicholaus Friedreich, professor of medicine in Heidelberg, Germany. Friedreich reported all the essential clinical and pathological features of the disease, a “degenerative atrophy of the posterior columns of the spinal cord” leading to progressive ataxia, sensory loss, and muscle weakness, often associated with scoliosis, foot deformity, and heart disease.

However, the subsequent description of atypical cases and of clinically similar diseases clouded classification for many years. Diagnostic criteria were established in the late 1970s, after renewed interest in the disease prompted several rigorous clinical studies. The Quebec Collaborative Group described the typical features of the disease in well-established cases. Harding modified some of the Quebec Collaborative Group’s diagnostic criteria to include cases at an early stage of the disease. According to Harding, the essential clinical features are (1) autosomal recessive inheritance, (2) onset before age 25 years, (3) progressive limb and gait ataxia, (4) absent tendon reflexes in the legs, and (5) electrophysiologic evidence of axonal sensory neuropathy, followed within 5 years of onset by (6) dysarthria, (7) areflexia at all 4 limbs, (8) distal loss of position and vibration sense, (9) extensor plantar responses, and (10) pyramidal weakness of the legs. While these criteria certainly identify the typical cases of FRDA, it is clear that this disease may show remarkable clinical variability, sometimes even within the same sibship, a rather uncommon finding for recessive disorders.

Clinical variability includes age of onset, rate of progression, and severity and extent of disease. Cardiomyopathy, kyphoscoliosis, pes cavus, optic atrophy, hearing loss, and diabetes mellitus occur only in some patients. Atypical cases with an overall FRDA-like phenotype but missing some of the essential diagnostic features can be identified. If these individuals have siblings with typical FRDA, they appear to represent extreme examples of the clinical spectrum of FRDA, but when they occur as isolated cases or cluster in families, their classification becomes uncertain. A variant clustering in families is Acadian FRDA, a clinical form with a milder course than classic FRDA and a lower frequency of cardiomyopathy that affects a specific population of French origin living in North America.
onset Friedreich ataxia (LOFA), with onset after age 25 years,16,17 and Friedreich ataxia with retained reflexes (FARR), in which tendon reflexes in the lower limbs are preserved,18 may cluster in families or occur in association with typical FRDA. The identification of the FRDA gene and of its most common mutation, the unstable hyperexpansion of a GAA triplet repeat sequence (TRS), has allowed physicians to reevaluate these issues on the basis of the results of molecular testing, with important consequences for the diagnostic criteria for FRDA.

THE FRDA GENE

The FRDA gene was assigned to chromosome 919,20; after fine mapping studies,21,22 a candidate region was defined and cloned.23-25 Only 1 gene, X25, was found in the minimum genetically defined candidate interval 26. The X25 gene has 7 exons spread over 95 kilobases (kb) of genomic DNA and is transcribed in the centromere to telomere direction. The first exon has a transcription start site preceded by several in-frame stop codons, and it harbors an unmethylated CpG island, containing several rare restriction sites. The most abundant transcript goes from exon 1 to 5a and has a size of 1.3 kb. Much less abundant isoforms contain exon 5b instead of 5a, sometimes followed by the noncoding exon 6. Their functional significance, if any, is still uncertain. The encoded protein was called frataxin.26

The FRDA gene demonstrates tissue-specific expression.26-28 In adult human tissues, its messenger RNA is most abundant in the heart, followed by the liver, skeletal muscle, and pancreas. In the central nervous system (CNS), it is highly expressed in the spinal cord, at lower levels in the cerebellum, and at very low levels in the cerebral cortex.26 The developmental expression of the gene has been investigated in the mouse by Northern blot analysis and RNA in situ hybridization.27,28 Very faint expression could be detected from embryonic day 10.5 in the neuroepithelium. At embryonic day 14.5 and into the postnatal period, frataxin was expressed at much higher levels. Maximum expression was observed in the spinal cord, particularly at the thoracolumbar level, and in the dorsal root ganglia (DRG). Significant levels of transcript could also be detected in the proliferating cells in the periventricular zone, in the cortical plates, in the heart, in the axial skeleton, and in some epithelial and mesenchymal tissues. In the adult animal, the expression of frataxin in the brain is reduced and mostly confined to the ependyma, while mRNA levels remain high in the spinal cord and DRG.

THE GAA TRIPLET REPEAT EXPANSION

Ninety-eight percent of FRDA chromosomes harbor an abnormal GAA repeat expansion within the first intron of the frataxin gene,26 which is localized within an Alu sequence 1.4 kb after exon 1. Normal chromosomes have 40 or fewer GAA triplets, while FRDA chromosomes have from approximately 100 to more than 1700 triplets. Hyperexpanded, disease-associated repeats are meiotically unstable20-31; ie, changes in the size of the GAA expansion are almost always observed in parent-child transmission to affected offspring and to carrier offspring. Paternal transmission is most often accompanied by a contraction of the repeat. Accordingly, in male carriers, smaller repeats are found in sperm than in leukocytes.29 Maternal transmission may result in further expansion or in contraction, with about equal probability.20-34 In addition to meiotic instability, the expanded GAA repeats show mitotic instability, causing somatic mosaicism for expansion sizes.30,31 This may be one reason for the residual and still remarkable phenotypic variability observed among individuals with almost identical GAA repeats as measured in peripheral blood leukocytes.

Expansion of the intronic GAA TRS inhibits the expression of the frataxin gene. This reduction has been shown at the RNA level as well as at the protein level; it is inversely proportional to the size of the expanded GAA repeats, particularly the smaller repeats.35,36

We cloned GAA TTC repeats containing 9 to 270 triplets into the intron of a 2-exon reporter gene contained in the plasmid pSPL3. Transient transfection experiments in COS-7 cells showed that transcription and replication of these plasmids are inhibited by the TRS in a length- and orientation-dependent manner; ie, long repeats that transcribe rGAA cause the highest inhibition of both processes.35 The GAA triplet expansion is a long DNA segment containing only purines (R) on one strand and pyrimidines (Y) on the complementary strand that may adopt a triple helical structure in the presence of DNA supercoiling.38-40 Such structure has been demonstrated for lengths of the GAA repeat found in FRDA chromosomes.41 Triplex structures have been shown to effectively inhibit transcription of the R-rich strand,42 suggesting a mechanism by which the expansion may suppress gene expression. Preliminary data show that a plasmid containing (GAA)130 demonstrates P1 nucleosome sensitivity indicative of an extensive single-stranded region spanning the entire TRS, as expected when a triple helical structure is adopted.

Clues about the origin of the GAA repeat expansions were obtained by investigating the GAA TRS in normal chromosomes. Normal alleles are distributed into a small normal group with 6 to 10 GAA triplets (83% of chromosomes in whites) and a large normal group with more than 13 triplets (17% of chromosomes in whites).32,33 Linkage dysequilibrium data indicate that disease-associated expansions arose from the large normal group of alleles.33 Large normal alleles containing uninterrupted runs of more than 34 GAA triplets have indeed been observed to undergo hyperexpansion to hundreds of triplets in a single generation.32,33 A few stable normal alleles with more than 34 triplets have been identified, but they are interrupted by a hexanucleotide repeat (GAGGAA), which probably has a stabilizing role.32,33 Therefore, as also proposed for myotonic dystrophy-associated CTG expansions,43 FRDA-associated GAA expansions seem to derive from a reservoir of at-risk alleles. The founding event in a population is then the generation of this at-risk group of alleles. Interestingly, preliminary observations in Japanese and Chinese subjects indicate that in these populations, neither GAA expansions (and therefore no Friedreich ataxia!) nor large normal alleles are found.
GENOTYPE-PHENOTYPE CORRELATIONS

According to several studies, earlier age of onset, earlier age confined to a wheelchair, more rapid rate of disease progression, and presence of nonobligatory disease manifestations indicative of more widespread degeneration show a direct correlation with the size of GAA repeats, particularly the smaller repeats. The likely reason for this correlation is that smaller expansions allow a higher residual expression of the frataxin gene and therefore determine a less profound deficiency of this protein. However, the sizes of the GAA expansions explain only about 50% of the variability in age of onset, indicating that other factors must influence the phenotype. In particular, we showed that patients with the milder Acadian variant of FRDA have expansions in the same size range as typical patients. In addition to the occurrence of somatic mosaicism for expansion sizes, variations in the frataxin gene itself, modifier genes, and environmental factors may all contribute to clinical variability.

Individuals homozygous for the FRDA-associated GAA expansions that do not have a phenotype matching the generally accepted diagnostic criteria have been identified in several studies. Most often, these patients have LOFA or FARR or a combination of the two, but occasionally even more atypical phenotypes have been reported, such as pure sensory ataxia and even chorea. Atypical FRDA may account for a small but significant proportion of cases with recessive or sporadic ataxia that do not fulfill the FRDA diagnostic criteria. Recently, 10% of patients in such a series were found to be homozygous for the FRDA GAA expansion.

POINT MUTATIONS

Missense, nonsense, and splice site mutations have been identified in about 2% of the FRDA chromosomes. The identification of point mutation has been essential in establishing that X25 is the FRDA gene. In all cases characterized thus far, affected individuals were heterozygous for their point mutation, had a normal frataxin coding sequence, but had an expanded GAA repeat on the other homologue of chromosome 9. The lack of homozygotes for point mutations may be a consequence of their rarity, but it is possible that homozygotes for frataxin null mutations are not observed because they have a very severe or lethal phenotype. Interestingly, a preliminary report on frataxin knockout mice suggested that these mutations may be embryonically lethal (M. Koenig, oral communication, September 1998).

Nonsense mutations have been found to cluster in a few spots, including the initiation ATG codon in exon 1, where mutations involving each of the nucleotides were identified, and a stretch of four Cs near the end of exon 1, where insertions or deletions occurred in several unrelated families. Missense mutations have been identified only in the C-terminal portion of the protein corresponding to the mature intramitochondrial form. Nonsense and most missense mutations result in a typical FRDA phenotype, while a few missense mutations, mostly in the less conserved, N-terminal portion of the mature form of frataxin, result in milder atypical phenotypes with slow progression. This suggests that the mutated proteins preserve some residual function. These findings may provide clues for the identification of functional domains of frataxin.

GENETIC HETEROGENEITY

We examined the segregation of highly polymorphic markers flanking the FRDA locus in 2 sibling pairs who had an FRDA-like phenotype (typical FRDA for 1 of the pairs) but no GAA expansions. We found a lack of linkage to chromosome 9q13. Our findings, as well as similar results reported by other groups, indicate the existence of some genetic heterogeneity for FRDA-like phenotypes. The fact that the FRDA locus could not be definitively excluded in other cases with no GAA expansions and no identifiable point mutations in the frataxin coding sequence leaves open the possibility that undetected gene abnormalities may underlie a minority of FRDA cases. In particular, the possibility of heterozygous deletions involving 1 or more exons in their entirety has not yet been investigated in these cases.

THE FUNCTION OF FRATAXIN

Frataxin's function could not be inferred from its amino acid sequence because no similarity with protein domains of known function could be detected. The protein shows a striking degree of evolutionary conservation, particularly in a stretch of 27 amino acids encoded by exons 4 and 5.

SUBCELLULAR LOCALIZATION

We demonstrated that frataxin is localized in mitochondria. Immunocytofluorescence with the monoclonal antifrataxin antibody 1G2 revealed granular cytoplasmic staining in various cultured cells: transfected COS-1 and HeLa cells overexpressing frataxin, mouse and human astroglial and neural cells, and human fibroblasts. Colocalization of 1G2 either with an autoimmune antimitochondrial antibody or with a mitochondrial-specific fluorescent dye (MitoTracker; Omega Optical Inc, Brattleboro, Vt) demonstrated the mitochondrial localization of frataxin. Independent support for mitochondrial localization came from Western blot analysis of cellular fractions obtained by differential centrifugation, which showed great frataxin enrichment in the mitochondrial pellet. Immunoelectron microscopy was performed on transfected HeLa cells and on human neural cells. Apparently, labeling was exclusively mitochondrial along the inner membrane. The negative control (omission of 1G2) was devoid of any electron-dense deposit. Further proof that frataxin is targeted to the mitochondria came from the analysis of the intracellular localization of fluorescent frataxin–green fluorescent protein (GFP) fusion proteins. A construct with GFP at the aminoterminus generated a diffuse cytosolic fluorescence consistent with the masking by GFP of a
frataxin aminoterminal mitochondrial targeting sequence. Constructs with frataxin or its first 20 amino acids at the aminoterminus generated fluorescence within organelar structures matching the appearance and distribution of mitochondria as revealed by specific staining.

The N-terminal mitochondrial targeting sequence of frataxin is proteolytically removed in a 2-step process. The first step involves the interaction of frataxin with the mitochondrial processing peptidase, which removes the first 40 amino acids. Twenty additional amino acids are removed in the second proteolytic step. At least in the case of the yeast homologous protein (yeast frataxin homolog [YFH1]), which is also mitochondrial, the latter step was shown to be promoted by a specific mitochondrial heat-shock protein of the hsp70 class, ssqlp. Yeast mutants with a defect of ssq1p process frataxin slowly and develop a phenotype similar to that of frataxin knockout mutants.

KNOCKOUT OF THE YEAST FRATAXIN HOMOLOG

Yeast frataxin homolog 1 is involved in iron homeostasis, as shown by the analysis of a YFH1 knockout yeast strain. Disruptants were obtained by the insertion of the HIS3 auxotrophic marker into the open reading frame of YFH1. The ΔYFH1 (yfh1::HIS3) strain was unable to grow on rich medium containing glycerol/ethanol (YPGE) as the carbon source, suggesting that ΔYFH1 was unable to carry out oxidative phosphorylation. Accordingly, ΔYFH1 showed a severe reduction in oxygen consumption, even in cells grown in rich medium; ΔYFH1 cells generate rho mutants with defects or loss of mitochondrial DNA. Measurement of iron content by atomic absorption spectroscopy revealed a doubling of iron content in ΔYFH1 cells and a 10-fold higher mitochondrial iron concentration compared with wild-type cells. No differences were observed in the mitochondrial content of copper or calcium. Such an increase in the mitochondrial iron level compared with a moderate increase in the total cell iron level indicates a decrease in cytosolic iron content. This results in a marked induction (10- to 50-fold) of the high-affinity iron transport system, which consists of a ferroxidase (Fet3p) and permease (Ftr1p), which are normally not expressed in cells that are replete with iron. Notably, the AFT1-1⁹⁰ strain, which has constitutive expression of the high-affinity iron transport system caused by a mutation in the transcriptional regulator AFT1 and shows intracellular iron levels comparable with those of the ΔYFH1 strain, does not show an increase in the mitochondrial iron level or a respiratory growth defect. This indicates that the accumulation of mitochondrial iron is specifically associated with the deletion of YFH1 and is not simply a consequence of increased cellular iron uptake. Excess iron in mitochondria, by reacting with oxygen, causes the oxidation of cellular components and ultimately and irreversibly damages the cell. Accumulation of mitochondrial iron in ΔYFH1 renders this strain hypersensitive to oxidative stress, as demonstrated by enhanced sensitivity to hydrogen peroxide compared with both wild-type and AFT1-1⁹⁰ cells.

RELEVANCE FOR THE PATHOGENESIS OF THE HUMAN DISEASE

If the yeast findings are relevant to the pathogenesis of FRDA, frataxin is a key element of the system controlling iron metabolism and free radical generation in the mitochondria. The involvement of iron in FRDA pathogenesis was previously suggested by the finding of deposits of this metal in the myocardial cells of patients with FRDA. Recent magnetic resonance imaging data indicate that iron also accumulates in an affected CNS structure, the dentate nucleus. Mitochondrial malfunction is compatible with the clinicopathological features of the disease; several mitochondrial abnormalities were proposed as the primary defect in FRDA, including lipooxidase dehydrogenase deficiency, pyruvate carboxylase deficiency, mitochondrial malic enzyme deficiency, and respiratory chain deficiencies. None of these observations has been confirmed or was consistently found in all patients. These studies were limited by the analysis of nonaffected tissues (liver, fibroblasts, muscle). Recently, Rotig et al demonstrated a reproducible respiratory chain deficiency in the heart, an affected organ in FRDA, involving respiratory complexes I, II, and III and both mitochondrial and cytosolic aconitases. All these enzymes and complexes contain iron-sulfur clusters in their active sites. Iron-sulfur proteins are remarkably sensitive to free radicals; their inactivation suggests oxidative stress in FRDA-affected tissues. In addition, cytosolic aconitase is involved in iron homeostasis and is converted to iron-responsive element binding protein (IRP-1) in response to low cytosolic iron levels, to oxidative radicals, and to signaling molecules, such as nitric oxide and carbon monoxide. The loss of cytosolic aconitase activity observed in FRDA might therefore reflect a switch of aconitase into IRP-1 in response to some of the above conditions, which could in turn affect the expression of several iron-regulated genes, enhancing iron uptake and reducing the levels of several iron-containing proteins.

Overall, there are several important points to be considered. Human patients with FRDA have only a partial frataxin deficiency, not a complete absence of protein as in the yeast model. Partial frataxin deficiency in FRDA cells is expected to cause a less dramatic mitochondrial iron accumulation than that observed in ΔYFH1 yeast cells. Cells in the human body seem not to have gross abnormalities or loss of mitochondrial DNA. Rather, they are likely to progressively accumulate oxidative damage and eventually become atrophic. In the nervous system, this applies to cell bodies as well as long axons. Reactive oxygen species (ROS) in mitochondria originate mostly from leakage at the level of complex III in the respiratory chain, where reduced ubiquinone (or, probably, its semiquinone form) may directly reduce molecular oxygen to superoxide (O₂⁻). It is estimated that 1% to 2% of oxygen may end up as superoxide in actively respiring cells. Superoxide has some toxic effects, but it is not considered a major cause of cell damage. Mitochondrial manganese-dependent superoxide dismutase (SOD2) usually takes care of superoxide, generating hydrogen peroxide, which in turn, in a reaction catalyzed by glutathione peroxidase, reacts with reduced glutathione, generating ox-
dized glutathione and water. Iron may intervene in this process and be engaged in a cycle with superoxide and hydrogen peroxide as follows:

\[
\text{Fe(III)} + \text{O}_2^- + 2\text{H}^+ \rightarrow \text{Fe(II)} + \text{H}_2\text{O}_2
\]

\[
\text{Fe(II)} + \text{H}_2\text{O}_2 \rightarrow \text{Fe(III)} + \cdot\text{OH} + \text{OH}^- 
\]

The above reactions lead to the production of the free hydroxyl radical, which is very short-lived because of its high reactivity, which leads to lipid peroxidation and protein and nucleic acid damage. Whether the free hydroxyl radical or the similarly reactive ferryl radical is produced by the Fenton reaction, as some authors suggest,64,65 the results are damaging for the cell. The Figure shows a simplified model of the abnormalities of iron and free radical metabolism that may be induced by frataxin deficiency.

In addition to the scavenging action of SOD2 and glutathione peroxidase, a front-line defense against free hydroxyl radical–induced lipid peroxidation is offered by vitamin E, 70% of which is localized in the inner mitochondrial membrane.63 Interestingly, vitamin E deficiency causes an FRDA-like disease.66

**THE PROBLEM OF SPECIFIC CELL VULNERABILITY**

The specificity of the pathologic characteristics of FRDA apparently reflects the distribution of frataxin.27,28 However, why frataxin, an essential protein in lower organisms, is not equally essential in all mammalian cell types is not yet known. One possibility is that it is indeed essential and that a complete lack would be incompatible with life, as is suggested by the lack of patients with FRDA without some residual amount of normal frataxin and by preliminary mouse Ro results. Nevertheless, the different levels of expression of the frataxin gene in different tissues indicate that the required amount of this protein is variable. Accordingly, preliminary results suggest that although an increase in mitochondrial iron may occur in all frataxin-deficient cells, including fibroblasts, it is much more marked in affected cells, such as cardiomyocytes.67 Human cell type specificity may relate to levels of respiratory activity (high in heart and CNS) and to levels of iron metabolism. However, expression of frataxin is not simply proportional to mitochondrial mass; in hu-
mans not much of this protein is made in mitochondria-rich tissues, such as the liver or the kidney. Cells that handle a lot of iron (eg, hemopoietic cells) do not seem to be particularly affected by frataxin deficiency, at least not at the clinical level. In addition, tissues composed of permanent cells may be more susceptible to a partial deficiency because they cannot replace damaged cells. Further factors must come into play; otherwise, it would be difficult to explain the specific vulnerability of the sensory system, while motor neurons are relatively spared. These are divided into factors that increase the mitochondrial generation of ROS, variations in protective systems against ROS of mitochondrial origin, and variations in the mechanism to handle mitochondrial iron.

FACTORS THAT INCREASE THE MITOCHONDRIAL GENERATION OF ROS

Factors that may increase mitochondrial ROS production include respiratory activity, iron uptake, iron storage, and production of signaling molecules with free radical properties, such as carbon monoxide and nitric oxide. Current data do not single out any of these factors as acting in particular in the target cells for FRDA. Respiratory activity is high in many neurons, including many untouched by FRDA. In this regard, in primates, the amount of cytochrome oxidase, an indicator of respiratory activity, is as high in some ventral horn motor neurons as in some DRG sensory neurons.

Furthermore, among cat DRG neurons, those with the highest complex II activity, another marker of oxidative capacity, are small neurons, a size not affected by FRDA. The neurons affected by FRDA are not known to have high production of nitric oxide or carbon monoxide. In the spinal cord and DRG of most species, nitric oxide is generated by intermediolateral column neurons (visceral effectors), by small neurons in the DRG, and by some neurons in the posterior horns, all spared by FRDA. Iron uptake in the brain is reported to be highest in the cerebellum, followed by the brainstem; the frontal, parietal, and occipital cortices; the hippocampus; and the caudate nucleus, in decreasing order.

Therefore, brain iron uptake seems to be higher in certain regions that show some involvement in FRDA, but these data need much further refinement for our purposes. The most important pathway for brain iron uptake seems to involve the binding of transferrin iron to transferrin receptors on endothelial cells, transport of iron to the interstitial space, binding to transferrin synthesized in the CNS, diffusion through the interstitial space and the cerebrospinal fluid, and, finally, internalization into cells carrying transferrin receptors, but transferrin-independent pathways are also operating. More than 30 years ago, a report suggested that brain iron uptake was increased in FRDA, but it was not followed by any similar study, and the study’s method, including the diagnostic criteria for FRDA, would not be considered adequate by today’s standards. As for iron storage, stainable iron is normally present particularly but not exclusively in the globus pallidus, caudate nucleus, substantia nigra, and dentate nucleus.

The amount of iron in some of these areas may be as high as in the liver, a very iron-rich organ. With the excep-

tion of the dentate nucleus, these areas (as well as the liver) are marginally affected or not affected in FRDA. Interestingly, however, the regional differences in iron storage in the brain not only do not match the distribution of FRDA pathology, they also do not match the rates of iron uptake.

VARIATIONS IN PROTECTIVE SYSTEMS AGAINST ROS OF MITOCHONDRIAL ORIGIN

Protective factors include enzymes for ROS scavenging; ferritin, which protects from the toxic effects of iron free radicals; and small antioxidant molecules, such as glutathione and vitamin E. Currently, the only clear-cut correlation between the distribution of these factors and FRDA pathology is the high degree of similarity on clinical and pathological grounds of FRDA and vitamin E deficiency. Because vitamin E is a scavenger of free radicals and particularly of free hydroxyl radicals, it is plausible that vulnerable cells have relatively fewer protective mechanisms that prevent the production of free hydroxyl radicals. In the mitochondrial compartment, these include SOD2 and mitochondrial glutathione peroxidase. Current data are not clear regarding how differences in these proteins relate to the distribution of vulnerable cells in FRDA. One extramitochondrial factor that might be considered is cytosolic copper- and zinc-dependent superoxide dismutase (SOD1). Mutations (probably causing a toxic gain of function) of this protein cause some cases of familial amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis specifically affects motor neurons that are spared in FRDA, while sparing the cells involved in FRDA. It may be that SOD1 is normally less active in cells that are more frataxin-dependent, so that these cells are protected against an SOD1 toxic gain of function; on the other hand, they will be more exposed to the failure of other antioxidant mechanisms, such as those involving frataxin and vitamin E.

VARIATIONS IN MECHANISM TO HANDLE MITOCHONDRIAL IRON

Frataxin is implicated in iron export from mitochondria, at least in yeast cells, so it is possible that a mechanism of cell vulnerability is related to heme synthesis. The final step of heme synthesis is performed in mitochondria. The subsequent export of heme may be an important system for iron export from mitochondria in some cell types. Frataxin may be less important for cells that export most mitochondrial iron in the form of heme iron. This mechanism could explain, at least in part, why organs very rich in iron and mitochondria, such as the liver, are spared in FRDA. Heme synthesis in the adult rat CNS is only 20% that in the liver. Within the CNS, heme synthesis is regulated differently than in erythroid cells; it may be related to the necessities of cytochromes and other hemoproteins, and it may also provide a substrate for heme oxygenase, the enzyme that generates the carbon monoxide signaling molecule.

All the available data suggest that an imbalance in the intracellular distribution of iron, with mitochondrial accumulation and relative cytosolic depletion rather than an over-
all accumulation of this metal, may be involved in the pathogenesis of FRDA. In the opinion of the author, these circumstances suggest caution before undertaking attempts at correction using iron chelators, such as deferoxamine mesylate. Chelators such as deferoxamine may effectively remove iron from the extracellular fluid and cytosolic compartments, but it is doubtful that they selectively remove this metal from the mitochondrial compartment. General iron depletion may not be of any advantage if the toxic excess of mitochondrial iron remains trapped in these organelles; it may even be detrimental. The fact that female patients with FRDA do not have any better disease course is suggestive in this regard. Further studies are needed to clarify these issues and should be carried out before any extensive human experimentation with iron chelators, such as deferoxamine.

The next challenge is to fully understand frataxin function, how its loss results in mitochondrial iron accumulation in some tissues and how the problem may be corrected. Finding proteins that interact with frataxin and developing mouse knockout models of frataxin deficiency constitute part of this challenge. For patients and their families, the possibility of developing a rational treatment for the disease may turn out to be a legitimate hope and no longer just an unrealistic dream.

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