ANTIOXIDANTS & REDOX SIGNALING
Volume 8, Numbers 3 & 4, 2006

Forum Review

Friedreich's Ataxia: From Disease Mechanisms to Therapeutic Interventions

RAFFAELE LODI,[1] CATERINA TONON,[1] VITTORIO CALABRESE,[2] and ANTHONY H.V. SCHAPIRA[3,4]

ABSTRACT

Friedreich's ataxia (FRDA) is the most common inherited ataxia. FRDA is an autosomal recessive degenerative disorder caused by a GAA triplet expansion or point mutations in the *FRDA* gene on chromosome 9q13. The FRDA gene product, frataxin, is a widely expressed mitochondrial protein that is severely reduced in FRDA patients. The function of frataxin has not been established yet. Studies of the yeast and animal model of the disease as well as of tissues from FRDA patients have demonstrated that deficit of frataxin is associated with mitochondrial iron accumulation, increased sensitivity to oxidative stress, deficit of respiratory chain complex activities and *in vivo* impairment of tissue energy metabolism. Pilot studies have shown the potential effect of antioxidant therapy in this condition and provide a strong rationale for designing larger clinical randomized trials. *Antioxid. Redox Signal.* 8, 438–443.

INTRODUCTION

Friedreich's ataxia (FRDA) is the commonest form of inherited ataxia with a prevalence of one or two in 40,000 individuals. FRDA is an autosomal recessive degenerative disorder characterized clinically by onset before the age of 25 of progressive gait and limb ataxia, cerebellar dysarthria, loss of limb deep tendon reflexes and position and vibration sense, spasticity, and extensor plantar responses (11, 16). Neuropathology in FRDA typically show early degeneration of large sensory neurons in the dorsal root ganglia, followed by degeneration of sensory posterior columns, spinal-cerebellar tracts, and cortical-spinal motor tracts, and atrophy of the large sensory fibers in peripheral nerves. Electrocardiographic or echocardiographic signs of hypertrophic cardiomyopathy are present in a large proportion of FRDA patients and cardiac involvement is the most common cause of premature death (11, 16). Left ventricular histological abnormalities consist of myocyte hypertrophy, diffuse fibrosis, and focal myocardial necrosis (1, 20, 42). Scoliosis and pes cavus are found in about two thirds and diabetes or glucose intolerance in one third (11, 16) of the patients. Hearing loss or optic atrophy is detected in about 10% of the patients.

In most cases FRDA is due to the inheritance of two copies of an expanded GAA triplet repeat in the first intron of the FRDA gene on chromosome 9q13 (8). The size of the expanded repeat is typically between 600 and 1200 triplets, but alleles ranging from 44 to 1700 triplets have been reported (11, 13, 14, 30). Normal chromosomes have *FRDA* gene alleles carrying between 8 and 22 triplet repeats (8). A smaller proportion of patients (<5%) are compound heterozygous, having one expansion-bearing chromosome and a deleterious point mutation in the *FRDA* gene of the other (8, 11).

The phenotypic variability among patients is heavily influenced by the size of the GAA expansion (11). In particular, the age at onset correlates negatively (11, 14, 24) and the rate of progression of the disease positively with the number of GAA repeats in the smaller allele (11). The frequency and severity of hypertrophic cardiomyopathy increase with the size of the GAA expansion in the smaller allele (11, 12, 14, 19).

[1]Dipartimento di Medicina Clinica e Biotecnologia Applicata, Universita' di Bologna, Bologna, Italy.
[2]Sezione di Biochimica e Biologia Molecolare, Dipartimento di Chimica, Università di Catania, Catania, Italy.
[3]University Department of Clinical Neurosciences, Royal Free and University College Medical School, and [4]Institute of Neurology, University College, London, United Kingdom.

Atypical clinical presentations, such as delayed age of onset (>25 years), retained deep tendon reflexes or hyperreflexia, slow disease progression, are often due to short and unstable GAA triplet repeat alleles (11, 14, 30).

PATHOPHYSIOLOGICAL FEATURES OF FRIEDREICH'S ATAXIA

Mutations in the *FRDA* gene, either GAA expansions or point mutations, result in reduced expression of a protein called frataxin (7) which localizes at mitochondrial membranes and crests (4, 7, 22, 32). In normal subjects, the highest level of expression of the *FRDA* gene has been found in the heart and spinal cord, intermediate levels in the cerebellum, liver, skeletal muscle, and pancreas, and very little in the cerebral cortex (8).The amount of residual frataxin in lymphoblastoid cell lines from FRDA patients correlates with the GAA expansion size in the smaller allele (7) and likely represents the molecular basis of the relationship between GAA expansion size and phenotypic expression of the disease (11).

The lack of frataxin is associated with mitochondrial dysfunction and intramitochondrial iron accumulation. Studies of yeast disrupted for *YFH1* (yeast frataxin homologue) gene have demonstrated that lack of the yeast frataxin homologue leads to a severe defect of mitochondrial respiration, loss of mitochondrial DNA, intramitochondrial iron accumulation, and increased sensitivity to oxidative stress (4, 15, 22, 44). Iron is a highly reactive species and is potentially toxic by virtue of its capacity to produce free oxygen radicals via iron-catalyzed Fenton chemistry. Excessive production of free radicals would damage lipids, proteins, and mtDNA. Accumulation of iron in the heart in FRDA was first demonstrated more than 20 years ago (23, 38) but only recently was it shown that the positive iron staining pattern in cardiac tissue from FRDA patients was granular in appearance and had a distribution consistent with mitochondrial iron accumulation (5). In the same study, iron accumulation was also found in hepatocytes and the spleen of FRDA patients. In cardiac muscle samples from FRDA patients collected by biopsy or at postmortem, reduced activities of respiratory chain complexes I, II, and III and of the Krebs cycle enzyme aconitase have been found (Fig. 1) (5, 36). These enzymes all contain iron-sulfur (Fe-S) clusters, and therefore frataxin could play a role in mitochondrial iron metabolism and the formation of Fe-S centers, or, alternatively, these enzymes may be targeted because of their particular sensitivity to damage by oxygen free radicals (36). In fibroblast lines from FRDA patients mitochondrial iron was increased by 40–50% (10, 45) while total cellular iron content was unchanged (10). Residual low levels of frataxin expression in human cells are likely to be responsible for the substantially less marked iron overload found in human tissues compared to that found in *YFH1* knockouts (4, 15). Fibroblasts from FRDA patients do, however, show an increased sensitivity to H_2O_2 and iron stress (45).

There are evidences of an impairment *in vivo* of glutathione homeostasis and antioxidant enzymes in patients with Friedreich's ataxia, suggesting a relevant role of free radical cytotoxicity in the pathophysiology of the disease. In

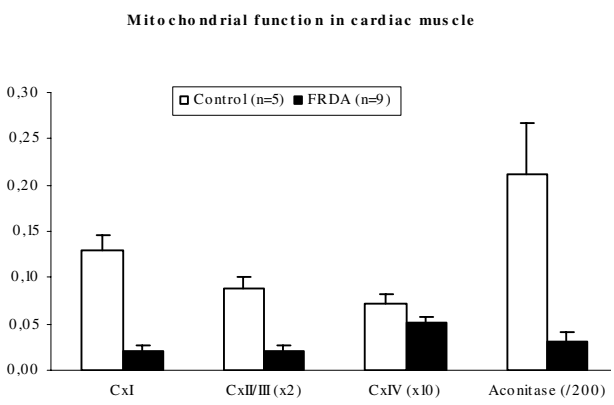

FIG. 1. Activities of respiratory chain complexes and aconitase assessed in the heart of patients with Friedreich's ataxia (FRDA) and controls. CxI, CxII/III, and CxIV represent citrate synthase (CS) ratios of mitochondrial respiratory chain complexes I, II/III, and IV, respectively. Values are expressed as means ± SEM.

fact, a reduction of free glutathione levels in the blood of patients with Friedreich's ataxia, a total glutathione concentration comparable to the controls, and a significant increase of glutathione bound to hemoglobin in erythrocytes have been demonstrated in FRDA patients (31), also associated with a significant elevation in the superoxide dismutase/glutathione peroxidase activity ratio and with an 83% rise of glutathione transferase activity in the blood (41).

Despite the increasing evidence that the deficit of frataxin is associated with impairment of mitochondrial oxidative phosphorylation and mitochondrial iron accumulation, frataxin function is still unknown. FRDA is an autosomal recessive disorder; therefore, animal models must be created by knockout or knockdown of the gene. Knockout of the frataxin gene leads to early embryonic death, indicating the importance of this gene in early development (9). Partial knockdown of frataxin resulting in 30–40% of protein production does not produce a clinical phenotype, indicating that a small residual amount of frataxin is sufficient for normal function. A conditional knockout mouse model of muscle frataxin leads to death at 10–12 weeks (33, 40). Abnormalities began at week 4 with a 50% reduction in complex II activity, cardiac function remained normal at this time. By week 5, however, there was an increase in left ventricular mass, left ventricular end systolic and diastolic diameter, and a 24% reduction in the shortening fraction. At week 6, cardiac output was down 15% and there was evidence of abnormal mitochondrial morphology. Week 7 showed a 67% decrease in shortening fraction and a surprising reduction in oxidized protein. By week 8, cardiac output was 67% of control, complex II activity was down 80%, but there was no evidence of mitochondrial iron accumulation. At week 9, mitochondrial iron was elevated but lipid peroxidation was decreased. Idebenone treatment 90 mg/kg/day delayed the onset of cardiac abnormalities by only one week and prolonged lifespan by 10%. The therapy had no protective effect on complex II activity.

The potential protective effect of antioxidant treatment in this murine model was assessed by overexpression of Cu-Zn superoxide dismutase (SOD) and a Mn SOD mimetic. However, there was no evidence of a protective effect on the development or severity of the cardiomyopathy, and no benefit on survival (39). Mn SOD protein expression fell by approximately 50% compared to controls in the heart at 10 weeks. There was no increase in oxidized protein levels in either heart or cerebellum. These results would suggest that frataxin deficiency does not lead to oxidative stress and alternative mechanisms may be involved in mediating the neurodegeneration associated with deficiencies of iron sulfur proteins.

IN VIVO TISSUE ENERGY METABOLISM IN FRIEDREICH'S ATAXIA PATIENTS

The effect of frataxin deficiency on tissue oxidative metabolism of FRDA patients has been assessed *in vivo* using phosphorus magnetic resonance spectroscopy (^{31}P-MRS). Magnetic resonance spectroscopy (MRS) is a noninvasive technique that allows, using clinical MR scanners, the measurement of several compounds as well as cytosolic pH *in vivo* without the use of radioactive tracers. The major compounds detectable are ATP, phosphocreatine (PCr), and inorganic phosphate (Pi) (Fig. 2). Free (metabolically active) [ADP], the major regulator of the oxidative phosphorylation, can be calculated from the MRS data using the creatine kinase equilibrium expression (3).

Cardiac bioenergetics were assessed *in vivo* in FRDA patients with and without left ventricular hypertrophy (27). Cardiac PCr to ATP ratios in the FRDA group as a whole were reduced by about 40% (Fig. 3). Cardiac PCr/ATP ratios were significantly reduced compared to controls in both groups of FRDA patients with normal and hypertrophic heart (27). These findings represented the first evidence in humans that cardiac PCr/ATP can be reduced in the absence of either failing contractile function or hypertrophy. In FRDA the hypertrophic process may be compensatory and caused or contributed to by the bioenergetics deficit, which is also known to stimulate myocyte hypertrophy (34). This hypothesis is supported by the frequent finding of hypertrophic cardiomyopathy in patients with a deficit of oxidative phosphorylation due to mutations of mitochondrial DNA (2).

Two independent ^{31}P-MRS studies of the calf muscle have shown a reduced rate of mitochondrial ATP synthesis in FRDA patients (25). This is a typical finding in patients with mitochondrial myopathies due to mtDNA mutations. The same studies also showed that the *in vivo* deficit of mitochondrial ATP synthesis rate was strongly dependent on the size of the GAA repeats in the smaller allele: the higher the number of GAA repeats the lower the mitochondrial ATP synthesis rate. This is clear evidence that the GAA expansion is the cause of the mitochondrial deficit and suggests a link between the degree of mitochondrial respiration deficit and clinical expression of the disease in other tissues. The length of the GAA expansion has been shown to determine the amount of frataxin expressed (7). Therefore, the residual expression of frataxin probably determines the

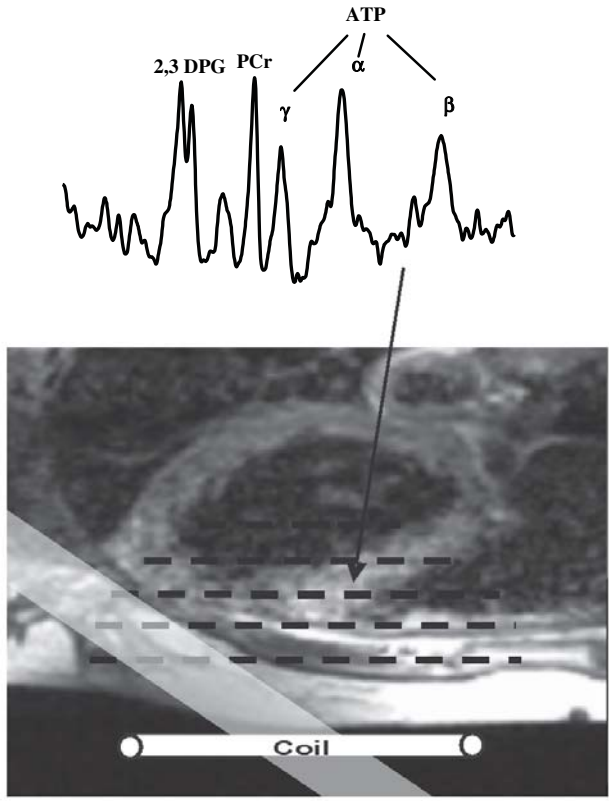

FIG. 2. Energy metabolism in Friedreich's ataxia. *Top:* ^{31}P-MRS cardiac spectrum collected from apex and part of the septum and posterior wall of a healthy subject. 2–3 DPG indicates 2–3 diphosphoglycerate, PCr phosphocreatine, and γ, α, and β, the three phosphate groups of ATP. *Bottom:* Axial MR image showing the location of the surface coil. Signal localization was achieved by slice selection (*transverse slice*), elimination of signal from anterolateral chest wall skeletal muscles using an oblique presaturation slab (*shaded region*) and phase encoding into 1 cm thick contiguous coronal slices (*dotted lines*).

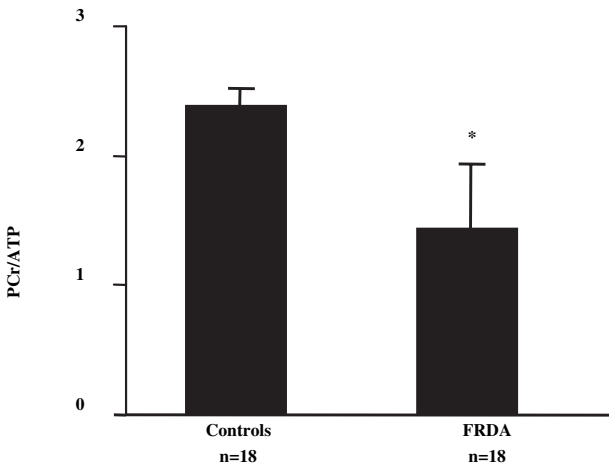

FIG. 3. Cardiac bioenergetics *in vivo*. Reduced cardiac phosphocreatine to ATP ratio (PCr/ATP) in Friedreich's ataxia (FRDA) patients. Values are expressed as means ± SD. *$p < 0.001$.

reduced skeletal muscle mitochondrial ATP production rate detected *in vivo*.

Consistently, noninvasive continuous near infrared muscle spectroscopy (NIRS), that assesses the delivery and utilization of oxygen in response to exercise, showed in several FRDA patients features consistent with inadequate oxygen utilization by muscle (28).

THERAPEUTIC PROSPECTIVE

The pathophysiological model of FRDA based on yeast and human studies (Fig. 4) indicates two possible therapeutic approaches: iron-chelation and antioxidant therapy. The possible role of iron-chelation therapy was recently evaluated (43). Serum iron, representing available tissue iron supply, and serum ferritin, representing total iron storage, were assessed in FRDA patients. The measurements were within the normal range in all FRDA patients indicating that iron-chelation therapy may not be beneficial to FRDA patients. These results are not entirely unexpected because in FRDA there is a redistribution of iron rather than an increase in total iron storage. Studies of the yeast model of FRDA have shown a small increase in total cellular iron levels in association with a 10–12 times increase in mitochondrial iron content (4, 15). Similarly, selective accumulation of intramitochondrial iron has been found in fibroblasts (10) and cardiac samples of FRDA patients (5). Taken together, these findings suggest that iron-chelation therapy may not be beneficial to FRDA patients unless targeting specifically mitochondrial iron. The potential role of iron chelators 2-pyridylcarboxaldehyde isonicotinoyl hydrazone (PCIH) analogues, as agents to remove mitochondrial iron deposits, have been recently under investigation (35). These ligands have been specifically designed to enter and target mitochondrial iron pools, which is a property lacking in desferrioxamine, the only chelator in widespread clinical use that because of its hydrophilicity would probably be prevented from access to mitochondria.

The excessive free radical production and deficit of oxidative phosphorylation shown in FRDA suggests that the mitochondrial respiration deficit may be amenable to treatment with antioxidants. In a few studies so far the effect of antioxidant therapy on cardiac and neurological symptoms/signs has been evaluated.

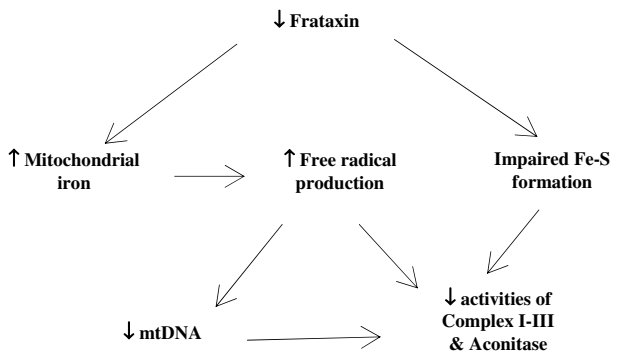

FIG. 4. Pathophysiological model. Schematic representation of the events associated with frataxin deficit and contributing to cell death in Friedreich's ataxia.

Three FRDA patients were first treated for 4 to 9 months with idebenone (5 mg/kg/daily), a short chain quinone analogue which acts as a free-radical scavenger (37). Idebenone administration resulted in a reduction in septal thickness ranging from 31% to 36% and of the left ventricle posterior wall from 8% to 20%. These results were then confirmed by the same group that showed a reduction in left ventricular mass equal or more than 20% in 17 out of 38 FRDA patients (18), and by two more recent idebenone trials (6, 29).

The effect of another antioxidant treatment, Coenzyme Q_{10}, 400 mg/day plus vitamin E, 2100 IU/day, on *in vivo* cardiac and calf muscle energy metabolism, left ventricle hypertrophy (LVH), and ataxia has been evaluated in ten FRDA patients (26). After 6 months of therapy, cardiac PCr to ATP ratio increased by more than 50% in the patients as a group. Skeletal muscle mitochondrial V_{max} for ATP production, after 6 months of CoQ_{10} and vitamin E treatment, increased by 34% in the patients' group.

Echocardiography showed unchanged interventricular septum and posterior wall thickness in patients with and without LVH. FRDA patients, assessed neurologically using the semiquantitative International Cooperative Ataxia Rating Scale (ICARS), showed lack of progression of their neurological deficits after 6 months of therapy (26). The followup of the same patients after 4 years of CoQ_{10} and vitamin E demonstrated a sustained improvement in cardiac and skeletal muscle bioenergetics throughout the therapy period (Fig. 5) and a significantly increased fractional shortening on echocardiography after the first 3 years of treatment (17). Comparison with cross-sectional data from 77 FRDA patients the change in total ICARS and kinetic scores over the period of the trial were better than predicted for 7 patients, but the posture and gait and hand dexterity scores progressed as predicted (17).

Antioxidants targeted to mitochondria appear to be a promising approach to slow disease progression. To validate this hypothesis, the efficacy of mitochondria-targeted and untargeted antioxidants derived from coenzyme Q10 and from vitamin E at preventing cell death due to endogenous oxidative stress has

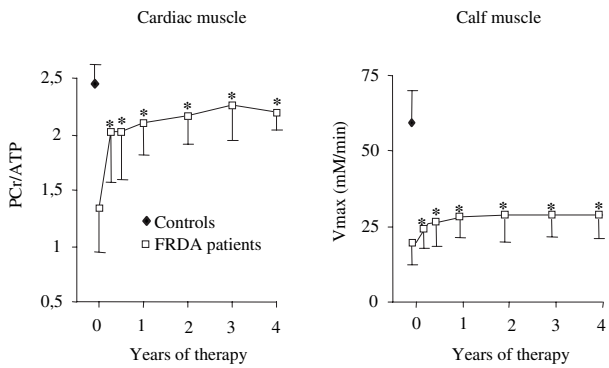

FIG. 5. Followup after Coenzyme Q_{10} plus vitamin E treatment. Cardiac phosphocreatine to ATP ratio (PCr/ATP) (*left*) and calf muscle maximum rate of mitochondrial ATP production (V_{max}) (*right*) in controls and Friedreich's ataxia (FRDA) patients before and after 3, 6, 12, 24, 36, and 48 months of antioxidant therapy (Coenzyme Q_{10} plus vitamin E). Values are expressed as means ± SD. *$p < 0.05$ compared to pre-therapy.

been recently investigated in cultured fibroblasts from FRDA patients in which glutathione synthesis has been blocked. The mitochondria-targeted antioxidant MitoQ was several hundred-fold more potent than the untargeted analog idebenone. The mitochondria-targeted antioxidant MitoVit E was 350-fold more potent than the water soluble analog Trolox (21). This is the first demonstration that mitochondria-targeted antioxidants prevent cell death caused by endogenous oxidative damage. Targeted antioxidants may have therapeutic potential in FRDA and in other disorders involving mitochondrial oxidative damage.

CONCLUSIONS

During the last decade, the progress made in our understanding of the pathogenic mechanisms underlying FRDA has been remarkable. Although the precise function of frataxin still remains to be defined, FRDA has clearly been identified as a nuclear-encoded mitochondrial disorder characterized by deficiency of activity of respiratory chain complexes and intramitochondrial iron accumulation. Preliminary clinical studies have indicated the potential efficacy of antioxidant therapy in this condition. However, larger randomized trials will have to confirm whether an early diagnosis of FRDA can be exploited to initiate antioxidant treatment and prevent the progression of this disorder.

ABBREVIATIONS

Fe-S, iron-sulfur; FRDA, Friedreich's ataxia; ICARS, International Cooperative Ataxia Rating Scale; LVH, left ventricle hypertrophy; PCIH, 2-pyridylcarboxaldehyde isonicotinoyl hydrazone; PCr, phosphocreatine; Pi, inorganic phosphate; ^{31}P-MRS, phosphorus magnetic resonance spectroscopy; SOD, superoxide dismutase.

REFERENCES

1. Alboliras ET, Shub C, Gomez MR, Edwards WD, Hagler DJ, Reeder GS, Seward JB, and Tajik AJ. Spectrum of cardiac involvement in Friedreich's ataxia: clinical, electrocardiographic and echocardiographic observations. *Am J Cardiol* 58: 518–524, 1986.
2. Antozzi C and Zeviani M. Cardiomyopathies in disorders of oxidative metabolism. *Cardiovasc Res* 35: 184–199, 1997.
3. Arnold DL, Taylor DJ, and Radda GK. Investigation of human mitochondrial myopathies by phosphorus magnetic resonance spectroscopy. *Ann Neurol* 18: 189–196, 1985.
4. Babcock M, DeSilva D, Oaks R, Davis-Kaplan S, Jiralerspong S, Montermini L, Pandolfo M, and Kaplan J. Regulation of mitochondrial iron accumulation by Yfh1p, a putative homolog of frataxin. *Science* 276: 1709–1712, 1997.
5. Bradley J, Blake J, Chamberlain S, Thomas P, Cooper J, and Schapira A. Clinical, biochemical and molecular genetic correlations in Friedreich's ataxia. *Hum Mol Genet* 9: 275–282, 2000.
6. Buyse G, Mertens L, Di Salvo G, Matthijs I, Weidemann F, Eyskens B, Goossens W, Goemans N, Sutherland GR, and Van Hove JL. Idebenone treatment in Friedreich's ataxia: neurological, cardiac, and biochemical monitoring. *Neurology* 60: 1679–1681, 2003.
7. Campuzano V, Montermini L, Lutz Y, Cova L, Hindelang C, Jiralerspong S, Trottier Y, Kish S J, Faucheux B, Trouillas P, Authier F J, Durr A, Mandel J L, Vescovi A, Pandolfo M, and Koeing M. Frataxin is reduced in Friedreich ataxia patients and is associated with mitochondrial membranes. *Hum Mol Genet* 6: 1771–1780, 1997.
8. Campuzano V, Montermini L, Molto' MD, Pianese L, Cassee M, Cavalcanti F, Monros E, Rodius F, Duclos F, Monticelli A, Zara F, Canizares J, Koutnikova H, Bidichandani SI, Gellera C, Brice A, Trouillas P, DeMichele G, Filla A, DeFrutos R, Palau F, Patel PI, DiDonato S, Mandel JL, Cocozza S, Koenig M, and Pandolfo M. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. *Science* 271: 1423–1427, 1996.
9. Cossee M, Puccio H, Gansmuller A, Koutnikova H, Dierich A, LeMeur M, Fischbeck K, Dolle P, and Koenig M. Inactivation of the Friedreich ataxia mouse gene leads to early embryonic lethality without iron accumulation. *Hum Mol Genet* 9: 1219–1226, 2000.
10. Delatycki MB, Camakaris J, Brooks H, Evans-Whipp T, Thorburn DR, Williamson R, and Forrest SM. Direct evidence that mitochondrial iron accumulation occurs in Friedreich ataxia. *Ann Neurol* 45: 673–675, 1999.
11. Durr A, Cossee M, Agid Y, Capuzano V, Mignard C, Penet C, Mandel JL, Brice A, and Koenig M. Clinical and genetic abnormalities in patients with Friedreich's ataxia. *N Engl J Med* 335: 1169–1175, 1996.
12. Dutka DP, Donnelly JE, Palka P, Lange A, Nunez DJ, and Nihoyannopoulos P. Echocardiographic characterization of cardiomyopathy in Friedreich's ataxia with tissue Doppler echocardiographically derived myocardial velocity gradients. *Circulation* 102: 1276–1282, 2000.
13. Epplen C, Epplen JT, Frank G, Miterski B, Santos EJ, and Schols L. Differential stability of the (GAA)n tract in the Friedreich ataxia (STM7) gene. *Hum Genet* 99: 834–836, 1997.
14. Filla A, DeMichele G, Cavalcanti F, Pianese L, Monicelli A, Campanella G, and Cocozza S. The relationship between trinucleotite (GAA) repeat length and clinical features in Friedreich ataxia. *Am J Hum Genet* 59: 554–560, 1996.
15. Foury F and Cazzalini O. Deletion of yeast homologue of the human gene associated with Friedreich's ataxia elicits iron accumulation in mitochondria. *FEBS Lett* 411: 373–377, 1997.
16. Harding AE. Friedreich's Ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. *Brain* 104: 598–620, 1981.
17. Hart PE, Lodi R, Rajagopalan B, Bradley J, Crilley J, Turner C, Blamire A, Manners D, Styles P, Schapira A, and Cooper J. Antioxidant treatment of patients with Friedreich's ataxia: 4 year follow up. *Arch Neurol* 62: 621–626, 2005.
18. Hausse AO, Aggoun Y, Bonnet D, Sidi D, Munnich A, Rotig A, and Rustin P. Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia. *Heart* 87: 346–349, 2002.
19. Isnard R, Kalotka H, Durr A, Cossee M, Schmitt M, Pousset F, Thomas D, Brice A, Koenig M, and Komajda M. Correlation between left ventricular hypertrophy and GAA

trinucleotide repeat length in Friedreich's ataxia. *Circulation* 95: 2247–2249, 1997.
20. James TN, Cobbs BW, Coghlan HC, McCoy WC, and Fisch C. Coronary disease, cardioneuropathy, and conduction system abnormalities in the cardiomyopathy of Friedreich's ataxia. *Br Heart J* 57: 446–457, 1987.
21. Jauslin ML, Meier T, Smith RA, and Murphy MP. Mitochondria-targeted antioxidants protect Friedreich ataxia fibroblasts from endogenous oxidative stress more effectively than untargeted antioxidants. *FASEB J* 17: 1972–1974, 2003.
22. Koutnikova H, Campuzano V, Foury F, Dolle' P, Cazzalini O, and Koenig M. Studies of human, mouse and yeast homologoues indicate a mitochondrial function for frataxin. *Nat Genet* 16: 345–351, 1997.
23. Lamarche JB, Cote M, and Lemieux B. The cardiomyopathy of Friedreich's ataxia morphological observations in 3 cases. *Can J Neurol Sci* 7: 389–396, 1980.
24. Lamont PJ, Davis MB, and Wood NW. Identification and sizing of the GAA trinucleotide repeat expansion of Friedreich's ataxia in 56 patients. Clinical and genetic correlates. *Brain* 120: 673–680, 1997.
25. Lodi R, Cooper JM, Bradley JL, Manners D, Styles P, Taylor DJ, and Schapira AHV. Deficit of *in vivo* mitochondrial ATP production in patients with Friedreich ataxia. *Proc Natl Acad Sci USA* 96: 11492–11495, 1999.
26. Lodi R, Hart PE, Rajagopalan B, Taylor DJ, Crilley JG, Bradley JL, Blamire AM, Manners D, Styles P, Schapira AH, and Cooper JM. Antioxidant treatment improves *in vivo* cardiac and skeletal muscle bioenergetics in patients with Friedreich's ataxia. *Ann Neurol* 49: 590–596, 2001.
27. Lodi R, Rajagopalan B, Blamire AM, Cooper JM, Davies CH, Bradley JL, Styles P, and Schapira AH. Cardiac energetics are abnormal in Friedreich ataxia patients in the absence of cardiac dysfunction and hypertrophy: an *in vivo* 31P magnetic resonance spectroscopy study. *Cardiovasc Res* 52: 111–119, 2001.
28. Lynch DR, Lech G, Farmer JM, Balcer LJ, Bank W, Chance B, and Wilson RB. Near infrared muscle spectroscopy in patients with Friedreich's ataxia. *Muscle Nerve* 25: 664–673, 2002.
29. Mariotti C, Solari A, Torta D, Marano L, Fiorentini C, and Di Donato S. Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial. *Neurology* 60: 1676–1679, 2003.
30. Montermini L, Richter A, Morgan K, Justice CM, Julien D, Castellotti B, Mercier J, Poirier J, Capozzoli F, Bouchard JP, Lemieux B, Mathieu J, Vanasse M, Seni MH, Graham G, Andermann F, Andermann E, Melancon SB, Keats BJ, Di Donato S, and Pandolfo M. Phenotypic variability in Friedreich ataxia: role of the associated GAA triplet repeat expansion. *Ann Neurol* 41: 675–682, 1997.
31. Piemonte F, Pastore A, Tozzi G, Tagliacozzi D, Santorelli F M, Carrozzo R, Casali C, Damiano M, Federici G, and Bertini E. Glutathione in blood of patients with Friedreich's ataxia. *Eur J Clin Invest* 31: 1007–1011, 2001.
32. Priller J, Scherzer CR, Faber PW, MacDonald ME, and Ab Y. Frataxin gene of Friedreich's ataxia is targeted to mitochondria. *Ann Neurol* 42: 265–269, 1997.
33. Puccio H, Simon D, Cossee M, Criqui-Filipe P, Tiziano F, Melki J, Hindelang C, Matyas R, Rustin P, and Koenig M. Mouse models for Friedreich ataxia exhibit cardiomyopathy, sensory nerve defect and Fe-S enzyme deficiency followed by intramitochondrial iron deposits. *Nat Genet* 27: 181–186, 2001.
34. Rabinowitz M. Overview on pathogenesis of cardiac hypertrophy. *Circ Res* 35: 3–11, 1974.
35. Richardson DR. Friedreich's ataxia: iron chelators that target the mitochondrion as a therapeutic strategy? *Expert Opin Investig Drugs* 12: 235–245, 2003.
36. Rotig A, Lonlay PD, Chretien D, Foury F, Koenig M, Sidi D, Munnich A, and Rustin P. Aconitase and mitochondrial iron-sulfur protein deficiency in Friedreich ataxia. *Nat Genet* 17: 215–217, 1997.
37. Rustin P, von Kleist-Retzow JC, Chantrel-Groussard K, Sidi D, Munnich A, and Rotig A. Effect of idebenone on cardiomyopathy in Friedreich's ataxia: a preliminary study. *Lancet* 354: 477–479, 1999.
38. Sanchez-Casis G, Cote M, and Barbeau A. Pathology of the heart in Friedreich's ataxia: review of the literature and report of one case. *Can J Neurol Sci* 3: 349–354, 1976.
39. Seznec H, Simon D, Bouton C, Reutenauer L, Hertzog A, Golik P, Procaccio V, Patel M, Drapier JC, Koenig M, and Puccio H. Friedreich ataxia: the oxidative stress paradox. *Hum Mol Genet* 14: 463–474, 2005.
40. Seznec H, Simon D, Monassier L, Criqui-Filipe P, Gansmuller A, Rustin P, Koenig M, and Puccio H. Idebenone delays the onset of cardiac functional alteration without correction of Fe-S enzymes deficit in a mouse model for Friedreich ataxia. *Hum Mol Genet* 13: 1017–1024, 2004.
41. Tozzi G, Nuccetelli M, Lo Bello M, Bernardini S, Bellincampi L, Ballerini S, Gaeta LM, Casali C, Pastore A, Federici G, Bertini E, and Piemonte F. Antioxidant enzymes in blood of patients with Friedreich's ataxia. *Arch Dis Child* 86: 376–379, 2002.
42. Unverferth DV, Schmidt WR, Baker PB, and Wooley CF. Morphologic and functional characteristics of the heart in Friedreich's ataxia. *Am J Med* 82: 5–10, 1987.
43. Wilson RB, Lynch DR, and Fischbeck KH. Normal serum iron and ferritin concentrations in patients with Friedreich's ataxia. *Ann Neurol* 44: 132–134, 1998.
44. Wilson RB and Roof DM. Respiratory deficiency due to loss of mitochondrial DNA in yeast lacking the frataxin homologue. *Nat Genet* 16: 352–357, 1997.
45. Wong A, Yang J, Cavadini P, Gellera C, Lonnerdal B, Taroni F, and Cortopassi G. The Friedreich's ataxia mutation confers cellular sensitivity to oxidant stress which is rescued by chelators of iron and calcium and inhibitors of apoptosis. *Hum Mol Genet* 8: 425–430, 1999.

Address reprint requests to:
Raffaele Lodi, M.D., Ph.D.
Dipartimento di Medicina Clinica e
Biotecnologia Applicata "D. Campanacci"
Universita' di Bologna
Policlinico S. Orsola
Via Massarenti 9
40138 Bologna, Italy

E-mail: raffaele.lodi@unibo.it

Received after final revision September 19, 2005; accepted September 20, 2005.

This article has been cited by:

1. H. Akhlaghi, L. Corben, N. Georgiou-Karistianis, J. Bradshaw, M.B. Delatycki, E. Storey, G.F. Egan. 2012. A functional MRI study of motor dysfunction in Friedreich's ataxia. *Brain Research* **1471**, 138-154. [CrossRef]
2. Haoran Li, Caryn E. Outten. 2012. Monothiol CGFS Glutaredoxins and BolA-like Proteins: [2Fe-2S] Binding Partners in Iron Homeostasis. *Biochemistry* **51**:22, 4377-4389. [CrossRef]
3. Felicity Klopper, Martin B Delatycki, Louise A Corben, John L Bradshaw, Gary Rance, Nellie Georgiou-Karistianis. 2011. The Test of Everyday Attention Reveals Significant Sustained Volitional Attention and Working Memory Deficits in Friedreich Ataxia. *Journal of the International Neuropsychological Society* **17**:01, 196-200. [CrossRef]
4. Yi-chung Lee, Yi-chu Liao, Po-shan Wang, I-Hui Lee, Kon-ping Lin, Bing-wen Soong. 2011. Comparison of cerebellar ataxias: A three-year prospective longitudinal assessment. *Movement Disorders* n/a-n/a. [CrossRef]
5. Vittorio Calabrese, Carolin Cornelius, Anna Maria Giuffrida Stella, Edward J. Calabrese. 2010. Cellular Stress Responses, Mitostress and Carnitine Insufficiencies as Critical Determinants in Aging and Neurodegenerative Disorders: Role of Hormesis and Vitagenes. *Neurochemical Research* **35**:12, 1880-1915. [CrossRef]
6. Isabelle Iltis, Diane Hutter, Khalaf O. Bushara, H. Brent Clark, Myron Gross, Lynn E. Eberly, Christopher M. Gomez, Gülin Öz. 2010. 1H MR spectroscopy in Friedreich's ataxia and ataxia with oculomotor apraxia type 2. *Brain Research* **1358**, 200-210. [CrossRef]
7. Robert F. English, José A. EttedguiCardiological Aspects of Systemic Disease 1163-1189. [CrossRef]
8. Josef Finsterer. 2010. Treatment of mitochondrial disorders. *European Journal of Paediatric Neurology* **14**:1, 29-44. [CrossRef]
9. Tina Wenz. 2009. PGC-1Î± activation as a therapeutic approach in mitochondrial disease. *IUBMB Life* **61**:11, 1051-1062. [CrossRef]
10. Gregory Jon Anderson, Christopher D. Vulpe. 2009. Mammalian iron transport. *Cellular and Molecular Life Sciences* **66**:20, 3241-3261. [CrossRef]
11. Janet M. Dubinsky. 2009. Heterogeneity of nervous system mitochondria: Location, location, location!. *Experimental Neurology* **218**:2, 293-307. [CrossRef]
12. Po Sing Leung , Yuk Cheung Chan . 2009. Role of Oxidative Stress in Pancreatic Inflammation. *Antioxidants & Redox Signaling* **11**:1, 135-166. [Abstract] [Full Text PDF] [Full Text PDF with Links]
13. Lalla Aicha Ba, Mandy Doering, Torsten Burkholz, Claus Jacob. 2009. Metal trafficking: from maintaining the metal homeostasis to future drug design. *Metallomics* **1**:4, 292. [CrossRef]
14. Y GO, D JONES. 2008. Redox compartmentalization in eukaryotic cells. *Biochimica et Biophysica Acta (BBA) - General Subjects* **1780**:11, 1273-1290. [CrossRef]
15. Tanja Schmitz-Hübsch, Thomas Klockgether. 2008. An update on inherited ataxias. *Current Neurology and Neuroscience Reports* **8**:4, 310-319. [CrossRef]
16. Robert Sutak, Xiangcong Xu, Megan Whitnall, Mohammed Abul Kashem, Daniel Vyoral, Des R. Richardson. 2008. Proteomic analysis of hearts from frataxin knockout mice: Marked rearrangement of energy metabolism, a response to cellular stress and altered expression of proteins involved in cell structure, motility and metabolism. *PROTEOMICS* **8**:8, 1731-1741. [CrossRef]
17. Joel M. Gottesfeld. 2007. Small molecules affecting transcription in Friedreich ataxia. *Pharmacology & Therapeutics* **116**:2, 236-248. [CrossRef]
18. Vittorio Calabrese, Cesare Mancuso, Agrippino Ravagna, Marzia Perluigi, Chiara Cini, Carlo De Marco, D. Allan Butterfield, Anna Maria Giuffrida Stella. 2007. In vivo induction of heat shock proteins in the substantia nigra following L-DOPA administration is associated with increased activity of mitochondrial complex I and nitrosative stress in rats: regulation by glutathione redox state. *Journal of Neurochemistry* **101**:3, 709-717. [CrossRef]
19. E. Trushina, C.T. McMurray. 2007. Oxidative stress and mitochondrial dysfunction in neurodegenerative diseases. *Neuroscience* **145**:4, 1233-1248. [CrossRef]
20. Vittorio Calabrese, Eleonora Guagliano, Maria Sapienza, Mariangela Panebianco, Stella Calafato, Edoardo Puleo, Giovanni Pennisi, Cesare Mancuso, D. Allan Butterfield, Annamaria Giuffrida Stella. 2007. Redox Regulation of Cellular Stress Response in Aging and Neurodegenerative Disorders: Role of Vitagenes. *Neurochemical Research* **32**:4-5, 757-773. [CrossRef]

21. Cesare Mancuso, Marzia Perluigi, Chiara Cini, Carlo De Marco, Anna Maria Giuffrida Stella, Vittorio Calabrese. 2006. Heme oxygenase and cyclooxygenase in the central nervous system: A functional interplay. *Journal of Neuroscience Research* **84**:7, 1385-1391. [CrossRef]

22. Vittorio Calabrese , Mahin D. Maines . 2006. Antiaging Medicine: Antioxidants and Aging. *Antioxidants & Redox Signaling* **8**:3-4, 362-364. [Citation] [Full Text PDF] [Full Text PDF with Links]