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Therapeutic Developments in Friedreich Ataxia

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Abstract

Friedreich ataxia is an inherited, severe, progressive neuro- and cardiodegenerative disorder for which there currently is no approved therapy. Friedreich ataxia is caused by the decreased expression and/or function of frataxin, a mitochondrial matrix protein that binds iron and is involved in the formation of iron-sulfur clusters. Decreased frataxin function leads to decreased iron-sulfur cluster formation, mitochondrial iron accumulation, cytosolic iron depletion, oxidative stress, and mitochondrial dysfunction. Cloning of the disease gene for Friedreich ataxia and elucidation of many aspects of the biochemical defects underlying the disorder have led to several major therapeutic initiatives aimed at increasing frataxin expression, reversing mitochondrial iron accumulation, and alleviating oxidative stress. These initiatives are in preclinical and clinical development, and are reviewed herein.

Keywords

Friedreich ataxia; mitochondria; iron; experimental therapeutics; trinucleotide repeat disorders

Friedreich ataxia, an autosomal recessive neuro- and cardiodegenerative disorder with a prevalence of approximately 1 in 50 000 in European populations, is characterized by progressive ataxia of all 4 limbs, dysarthria, areflexia, sensory loss, and muscle fatigability. The neurological signs and symptoms are largely secondary to degeneration of the large sensory neurons of the dorsal root ganglia and spinocerebellar tracts. Skeletal deformities and cardiomyopathy are found in most patients, impaired glucose tolerance and diabetes mellitus are found in ~30% of patients, and reduced visual acuity and hearing loss are occasionally seen.[1] Onset of symptoms usually occurs around puberty and most patients are confined to a wheelchair by their late 20s. Myocardial failure and/or arrhythmias are the most common cause of premature death.

Currently, no drugs are approved to treat Friedreich ataxia and the resultant disability, to prolong the life of a patient with Friedreich ataxia, or to cure the disorder. Three biochemical defects guide most current approaches to therapeutic development for Friedreich ataxia: (1) decreased expression of the disease gene, *FXN*, (2) mitochondrial iron accumulation, and (3) oxidative stress. In this review, I present an overview of some of the major therapeutic initiatives based on these 3 biochemical defects, discussing each in turn. For a more comprehensive review of experimental therapeutics for Friedreich ataxia, the

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reader is referred to the excellent recent reviews by Santos and colleagues,[2] Schmucker and Puccio,[3] and Pandolfo.[4]

Decreased Frataxin Expression

Friedreich ataxia is caused by intronic GAA repeat expansions in the *FXN* gene, which encodes the protein frataxin. Most patients with Friedreich ataxia (~96%) have expansions of a GAA repeat in the first intron of both alleles of *FXN*.[5] Normal alleles have 36 or fewer GAA repeats, while disease alleles have from approximately 70 to more than 1700 repeats.[6] The repeat expansions interfere with transcription of the protein frataxin,[7,8] and the size of the expansions correlate inversely with age of onset, and directly with rate of disease progression.[1] A complete knockout of the murine frataxin gene causes embryonic lethality, indicating that at least some frataxin function is necessary for survival.[9]

Because the *exonic* sequences of most disease alleles are intact, increasing frataxin expression is an attractive therapeutic target. The mechanism(s) by which GAA repeat expansions decrease expression of *FXN* include(s) hypoacetylation of histones H3 and H4, leading to the possibility that histone deacetylase inhibitors, which can change silent heterochromatin to an active chromatin conformation, might increase frataxin expression. Data supporting this possibility have been reviewed by Gottesfeld,[10] who pioneered the approach. Briefly, histone deacetylase inhibitors have been found that increase frataxin expression in blood lymphocytes of individuals with Friedreich ataxia in vitro,[11] and in vivo in transgenic mice carrying a GAA repeat expansion in the first intron of the murine frataxin gene, without acute toxicity.[12] The RepliGen Corporation (Waltham, MA) is now advancing lead-candidate histone deacetylase inhibitors through preclinical toxicity studies and into phase 1 clinical trials for Friedreich ataxia.

Recombinant human erythropoietin increases frataxin expression in primary Friedreich ataxia lymphocytes and fibroblasts,[13] without increasing *FXN* mRNA, suggesting a posttranscriptional effect.[14] In open-label, pilot trials of erythropoietin, frataxin expression in blood lymphocytes increased by a mean of 27% ($P < .01$) after 8 weeks of treatment in 7 of 11 individuals with Friedreich ataxia,[15] and Ataxia Rating Scale scores improved after 6 months of treatment.[16] In the latter study, 4 of 8 patients required phlebotomy for elevated hematocrit. Because erythropoietin is an endogenous agonist, cellular regulatory mechanisms might result in desensitization with chronic treatment. In addition, chronic treatment is sometimes associated with a pure red cell aplasia.[17–20] In a study of larger single doses of erythropoietin for Friedreich ataxia, a delayed but significant increase in frataxin was noted after 3 months (1 dose) and 6 months (2 doses), and these doses were well-tolerated, although Ataxia Rating Scale scores were unchanged from baseline.[21] Erythropoietin mimetics, which might increase frataxin expression without a concomitant increase in hematocrit, are also under investigation.

The PPARγ coactivator PGC-1α is downregulated in human Friedreich ataxia cells and Friedreich ataxia mouse models,[22] supporting an approach proposed by Rustin,[23] which is to treat individuals with Friedreich ataxia with the commercially available PPARγ agonist pioglitazone, a diabetes drug.[24] A proof-of-concept trial of pioglitazone for the treatment of Friedreich ataxia is in progress in France. Other approaches to increase frataxin include high-throughput drug screens using a frataxin reporter system to identify compounds that increase frataxin expression (in progress); resveratrol, which increases frataxin expression in multiple in vitro Friedreich ataxia models (Joseph P. Sarsero, Fourth International Friedreich's Ataxia Conference Abstracts, www.curefa.org); and protein replacement therapy. In their approach to protein replacement, Vyas and colleagues found that a fusion of frataxin with the protein transduction domain of the TAT protein (TAT-Frataxin)

successfully delivered frataxin to mitochondria in cultured cells from patients and in a severe mouse model of Friedreich ataxia.[25] Injection of TAT-Frataxin into a conditional-knockout mouse model developed by Puccio and colleagues[26] improved growth, increased lifespan by 53%, increased cardiac function, and improved biochemical abnormalities associated with loss of frataxin.[25]

Mitochondrial Iron Accumulation

Frataxin localizes to the mitochondrial matrix, where it binds iron and is involved in iron-sulfur cluster assembly.[27,28] Iron-sulfur clusters are prosthetic groups important for the function of many proteins, both mitochondrial and cytosolic, including aconitase and mitochondrial respiratory complexes I, II, and III. The decrease in frataxin function in Friedreich ataxia results in decreased iron-sulfur cluster assembly; in Friedreich ataxia patients, as well as in yeast and mouse models, this is associated with mitochondrial iron accumulation, cytosolic iron depletion, increased oxidative stress, and mitochondrial dysfunction.[26,29–42] Because the cellular pathophysiology of Friedreich ataxia includes iron dysregulation and mitochondrial iron accumulation, siderophores are of interest as possible therapeutics for Friedreich ataxia.[43–46]

The most-studied siderophore in the Friedreich ataxia field is deferiprone, a lipid-soluble 1,2-diketo heterocycle that chelates iron. In HEK-293 cells in which *FXN* mRNA was knocked down by RNAi, 50 μM deferiprone increased mitochondrial membrane redox potential, adenosine triphosphate production, and resistance to staurosporine-induced apoptosis.[42] By these measures, deferiprone outperformed the siderophores deferasirox, salicylaldehyde isonicotinoyl hydrazone, and deferoxamine. The affinities of deferiprone, deferasirox, salicylaldehyde isonicotinoyl hydrazone, and deferoxamine for iron (in pM at pH 7.4 for Fe^{3+}) are 19.5, 22.5, 27.7, and 26.6, respectively; ie, the order of efficacies in the HEK-293 Friedreich ataxia model (deferiprone > deferasirox = salicylaldehyde isonicotinoyl hydrazone > deferoxamine) correlated inversely with iron affinity, suggesting that a lower affinity for iron might be more efficacious.[42]

In a small, open trial for 11 Friedreich ataxia patients, deferiprone decreased brain iron by magnetic resonance imaging (MRI).[46] Waldvogel and colleagues had previously observed an increase in iron in the dentate nucleus of the brain in Friedreich ataxia patients using T2-weighted MRI;[47] however, Koeppen and colleagues later demonstrated that total iron in the dentate nucleus of patients with Friedreich ataxia was no different than that of normal controls, and that the signal depression on T2-weighted MRI (due to the paramagnetic effect of iron) was likely due to a shift of iron into ferritin in non-neuronal cells.[48] In another open-label trial, deferiprone was given to 20 individuals with Friedreich ataxia for 11 months, in combination with the antioxidant idebenone (see below); Ataxia Scale scores remained unchanged, which was interpreted as a stabilization of neurological function (since Ataxia Scale scores usually progress significantly over 11 months), and cardiac wall thicknesses decreased.[49]

A double-blind, randomized, placebo-controlled phase 2 trial of deferiprone for 80 individuals with Friedreich ataxia was recently completed. In a preliminary report (Arpa and colleagues, Fourth International Friedreich's Ataxia Conference Abstracts, www.curefa.org), there were no significant overall changes in Ataxia Scale scores, though improvements in posture, gait, and kinetic function were noted in some patients, and treatment was associated with a decrease in left ventricular mass. Low serum ferritin levels were noted in some patients, and there was one case of neutropenia, which resolved on drug withdrawal. (Deferiprone is associated with agranulocytosis in a subset of patients, necessitating weekly blood counts for anyone taking this experimental therapeutic.)

Oxidative Stress

The evidence for oxidative stress in Friedreich ataxia is the subject of an excellent recent review by Armstrong and colleagues.[50] That there should be oxidative stress in Friedreich ataxia, and that it might be difficult to measure directly, is unsurprising. The iron that accumulates in the mitochondria of cells with decreased frataxin function is primarily ferrous. Ferrous iron can generate toxic reactive oxygen species by reducing oxygen to the superoxide radical and reducing hydrogen peroxide to the extremely reactive hydroxyl radical (the Fenton reactions).[51] However, a certain level of physiologic reactive oxygen species is present normally, which can obscure low-level signals from a relatively small number of affected disease cells, and cells with extremes of oxidative stress often die by apoptosis. In the view of this author, the preponderance of evidence, both direct and indirect, supports the hypothesis that oxidative stress contributes to Friedreich ataxia pathophysiology, and thus supports the investigation of antioxidant approaches to treatment.

Idebenone, a short-chain parabenzoquinone derivative with a structure very similar to that of coenzyme Q10, advanced to phase 3 trials for Friedreich ataxia. Like coenzyme Q10, idebenone transfers electrons from complex I and complex II to complex III in the mitochondrial electron transport chain.[52] Open trials and small double-blind placebo-controlled trials indicated some indirect evidence for efficacy of idebenone for the cardiomyopathy of Friedreich ataxia, but little evidence for efficacy for the ataxia of Friedreich ataxia.[53–56] In phase 3 trials of idebenone, and in open-label extension studies, there were trends toward improvement in Ataxia Scale scores and cardiac hypertrophy, but statistical significance was not achieved.[57–59] In all of these studies of idebenone, the drug was safe and well-tolerated.

A number of other antioxidants are in preclinical and early clinical development, though little is published as yet regarding evidence for effectiveness in Friedreich ataxia. These antioxidants include EPI-A0001 and EPI-743, both being developed by Edison Pharmaceuticals; Egb-761, a Ginkgo biloba extract being developed by Ipsen; OX1, which is being developed by Intellect Neurosciences and may act as both an antioxidant and an iron chelator; mitochondrial radical quenchers, under development by Sid Hecht and colleagues at Arizona State University; and deuterated polyunsaturated fatty acids, which are reinforced against free-radical damage and are under development by Retrotope, Inc. (Los Altos Hills, CA).

Conclusion

Cloning of the disease gene for Friedreich ataxia and elucidation of many aspects of the biochemical defects underlying the disorder have led to an explosion of therapeutic initiatives. Ultimately, a combination of therapeutics aimed at each of the 3 categories described above — decreased frataxin expression, mitochondrial iron accumulation, and oxidative stress — may be most effective. The rationale for such a combination approach is that each drug will contribute to efficacy, while balancing side effects (which are inevitable with any drug). Regardless, because therapeutic development is often fraught with unexpected difficulties, the sheer number of initiatives for Friedreich ataxia bodes well for the successful development and approval of effective therapies during the next few years.

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