FEBS Letters

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# Friedreich's ataxia: Twenty years later

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| Journal: | *FEBS Letters* |
| Manuscript ID | Draft |
| Wiley - Manuscript type: | Special Issue |
| Date Submitted by the Author: | n/a |
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| Abstract: | Oxidative stress and increase of levels of free radicals are important markers associated to several pathologies, including Alzheimer's disease, cancer and diabetes. Among these pathologies is Friedreich's ataxia, a rare genetic neurodegenerative disease which involves the partial silencing of the small mitochondrial protein frataxin. Until the gene implicated was identified in 1996, frataxin had completely escaped our attention. More than twenty years after we now know how important this protein is being essential and part of the vital machinery which produces iron-sulfur clusters in the cell. In this review we revisit the most important steps which have brought us to our current understanding of the function of frataxin and its role in disease. Friedreich's ataxia is an excellent paradigmatic example of the problems proposed by the study of oxidative stress in disease. We review the existing animal and cellular models of Friedreich's ataxia and discuss specifically new techniques which can assist to study the disease mechanisms and reconstruct the role that oxidative stress plays in this pathology. |
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# Friedreich's ataxia: Twenty years after

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**Keywords**: frataxin, mitochondrial diseases, neurodegeneration, oxidative stress, triplet expansion

**Running title:** Friedreich's ataxia, twenty years later

**Abstract**

Oxidative stress and increase of levels of free radicals are important markers associated to several pathologies, including Alzheimer's disease, cancer and diabetes. Among these pathologies is Friedreich's ataxia, a rare genetic neurodegenerative disease which involves the partial silencing of the small mitochondrial protein frataxin. Until the gene implicated was identified in 1996, frataxin had completely escaped our attention. More than twenty years after we now know how important this protein is being essential and part of the vital machinery which produces iron-sulfur clusters in the cell. In this review we revisit the most important steps which have brought us to our current understanding of the function of frataxin and its role in disease. Friedreich's ataxia is an excellent paradigmatic example of the problems proposed by the study of oxidative stress in disease. We review the existing animal and cellular models of Friedreich's ataxia and discuss specifically new techniques which can assist to study the disease mechanisms and reconstruct the role that oxidative stress plays in this pathology.

## Introduction

Free radicals are molecules with free spared electrons which make the molecule highly reactive and thus dangerous. They are by-products of normal cell function. The cell contains a number of mechanisms to absorb and neutralize them. However, when these mechanisms are overwhelmed or insufficient, free radicals can cause harm by inducing oxidation of proteins and other essential molecules and induce damage. Free radicals can be generated by diet, stress, smoking, alcohol, exercise, inflammation, drugs, or exposure to the sun or air pollutants. Oxidative stress may contribute to the development of many diseases and chronic conditions, including cancer, neurodegeneration, and diabetes. In this review we focus on Friedreich's ataxia (FRDA), a rare mitochondrial neurodegenerative disease which constitutes an excellent example of a pathology associated to the presence of iron deposits and oxidative stress (reviewed in [1]). We will review the state of the field paying particular attention to the animal and cellular models which have been developed to study the role of free radicals and oxidative stress in this disease and suggest new strategies to study their development in disease aetiology and progression. For other aspects we will refer the reader to other more specific reviews.

## Phenotype and genetic causes of Friedreich's ataxia

Patterns of one or more nucleotide repeats are common in genomes (for a review see [2]). These regions can be subjected to genomic instability which results in their expansions and, in some cases, cause disease. The vast majority of these pathologies have neurological and/or developmental effects. Among the neurological diseases caused by a triplet expansion is FRDA, an autosomal recessive disease which causes progressive damage to the nervous system resulting in symptoms ranging from gait disturbance and speech problems to heart disease. It was named after the physician Nikolaus Friedreich, who first described the condition to the medical community in 1863 [3-6]. FRDA is characterized mainly by a progressive degeneration of large sensory neurons and cardiomyopathies [7]. Although rare, FRDA is the most frequent inherited ataxia, with an estimated prevalence of 2-4 people in 100,000 individuals and a carrier frequency of approximately 1:90 to 1:60 with prevalence in white populations. Most FRDA carriers and affected FRDA patients are believed to originate from a common European ancestor who lived more than 10,000 years ago [3, 8, 9]. FRDA symptoms usually begin between the age of 5 and 15 but can, on rare occasions, appear as early as 18 months or as late as 50 years of age. The first symptom usually is gait or difficulty

in walking. The ataxia gradually worsens and slowly spreads to the arms and then to the trunk. Sometimes, foot deformities may be early signs. Gradually muscles begin to weaken and waste away, especially in the feet, lower legs, and hands. Another symptom is the loss of tendon reflexes and, often, a gradual loss of sensation in the extremities, which may spread to other parts of the body. Rapid, rhythmic, involuntary movements of the eyes are common. Most FRDA patients develop scoliosis, which, if severe, may impair breathing and dysarthria making the patients easily fatigued. Other symptoms that may occur include chest pain, shortness of breath, and heart palpitations. These later symptoms are a consequence of the heart diseases that are associated with FRDA, such as cardiomyopathy. About 20% of people with FRDA develop carbohydrate intolerance and 10% develop diabetes mellitus. As a consequence, some people lose hearing or eyesight. The second anniversary of the discovery of the FRDA gene was in 2016. The gene was identified on chromosome 9q21.11 by positional cloning. A pathological expansion of a GAA-TTC repeat in the first intron of the locus *X25*, later named *FXN* (HGNC: 3951), has been detected in 98% of the affected alleles [10]. The expanded intronic alleles interfere with *FXN* transcription through epigenetic modifications, decreasing the production of normally functioning frataxin to 5-20% of the normal levels. The age of disease onset, its severity, rate of progression, and extent of neurological involvement vary with the number of repetitive GAA sequences. The larger the number of repeats, the more profound is the reduction in frataxin expression and thus the disease symptoms. The critical pathologic triplet threshold repeat in FRDA is 66 repeats, with the average expansion being of ~630 GAA repeats on the smaller alleles and ~890 GAA repeats on the larger ones. In FRDA patients, expression of *FXN* mRNA is decreased to 33% and the translated protein to 25% as compared to controls. Frataxin is expressed in all cells of eukaryotic organisms. However, mRNA levels and frataxin expression have tissue specificities that partially correlate with the organs mostly affected by the disease. In humans, the highest levels of expression are found in the heart and spinal cord, whereas lower levels are seen in the cerebellum, liver, skeletal muscle, and pancreas. The differential sensitivity of tissues to frataxin deficiency remains unclear as also the epigenetic factors which determine the severity of the disease: not always the protein levels correlate with disease severity [11].

**Searching for the frataxin function**

Frataxin is a small (210 amino acids) protein localized in the inner mitochondrial membrane [10]. It is synthesized in the cytosol as a precursor protein (1-210), matured in two steps

within the mitochondrial matrix to give an intermediate (42-210) and a mature form (81-210) [12]. The structure of frataxin was first established by nuclear magnetic resonance (NMR) spectroscopy for human frataxin (92-210) [13] (**Figure 1A**). The crystal structures of human, yeast and Escherichia coli frataxins were also published [14-16] although the yeast one had to be revised more recently and shown to be partially based on wrong spectral assignment [17]. They all share a very similar fold, which directly reflects a high degree of sequence conservation and strongly suggests a common function. The fold of the conserved core consists of a globular, slightly elongated domain in which two N- and C-terminal alpha helices pack against a central beta sheet. Conservation throughout species indicated which residues are essential, either for folding or for function: conserved and semi conserved residues cluster onto the same surface [13]. Frataxins are unusual iron-binding proteins that achieve iron coordination solely through glutamates and aspartates which cluster mostly on the first helix and are exposed on the protein surface, instead of the more common cysteines or histidines [18, 19]. CyaY and Yhf1, bacterial and yeast frataxins respectively, were shown to bind two $Fe^{2+}$ ions. Monomeric CyaY can bind up to six $Fe^{3+}$ ions [20]. Additional weaker binding sites allow further loading of 25 to 26 cations per monomer. Another unusual property is the apparent lack of selectivity. CyaY and, to a minor extent, human frataxin are able to bind all sort of divalent and trivalent cations, ranging from $Ca^{2+}$ and $Co^{2+}$ to $Al^{3+}$ and various lanthanides [18]. All of these cations compete for the same binding sites. It is now an important established fact that frataxin is an active component of the iron-sulfur cluster biogenesis machine, an essential metabolic pathway found in all organisms [21, 22]. Direct interaction between frataxin and the NFS1/IscU complex, the two central components of the iron-sulfur cluster biogenesis machine, was shown in several species (**Figure 1B,C)** which results in a regulatory effect of frataxin on the enzymatic formation of the clusters (for a review see [23]).

**The time dimension of FRDA**

An important aspect for understanding FRDA is to determine the time evolution of this disease. This is a theme of high general interest which concerns all diseases: it is often difficult to distinguish between causes, effects and co-existing phenomena in a disease. One could for instance wonder whether a certain symptom, say a back pain, is what determines a head ache or rather the two problems co-occur by chance. Understanding this relationship is essential because, in treatment, we would like to address directly the causes and not the side effects. FRDA does not escape this rule: despite having been extensively studied, it is still

unclear whether oxidative stress is a primary cause or a secondary effect which occurs as a by-product. The difficulty of answering to this question comes from the fact that patients' samples, which are our primary source of knowledge, have been exposed to the pathological condition for years since birth. Thus, when analysed they can only reveal an advanced state. A way around to clarify the scene is to develop inducible cellular or animal models which could allow us to knock-out, knock-down and overexpress the frataxin gene starting from a well-defined initial time point from which the phenotype can be induced [24]. New tools have appeared to assist this problem and follow the causal progression of disease by genome editing which can allow us to produce complex cell models where specific genes can be switch on and off at will. There are at least three main methodologies: 1) zinc finger nucleases (ZFN) [25], 2) the transcription activator-like effector nuclease or TALEN [26] and 3) the clustered regularly interspaced short palindromic repeats or CRISPR which, together with an RNA guided DNA endonuclease enzyme, seem to be the widely used frontier [27].

Different models of FRDA are now available in yeast, fly, worm, mouse and human cells which we will now discuss in some detail. The main phenotypes found in the different cell/animal models are summarised in **Table 1**. They have provided useful indications which can however lead to different conclusions. Their discrepancies are probably the consequence of the nature of the chosen cells/organism and the biomarkers used. Another important factor of difference that could explain the different responses is the time frames over which the phenotype progression is followed: this was for instance 0-72 hours in a yeast model [28], 0-12 days in Drosophila [29] and 0-10 days in mice [30]. Due to the wide range of phenotypes found in the different models, we will try to group the existing models by the animal/cell type.

**Yeast models**

Being one of the most characterised eukaryotic cells, yeast has been extensively used as a FRDA model thanks to its simplicity as a cell model and to the wide homology between human frataxin and yeast homologue, Yfh1. This simple organism is also particularly suited for temporal studies where the effects of frataxin depletion on the metabolism can be followed from the early phenotype onset onwards. One of the very first yeast models to take advantage of an inducible *YFH1* gene was developed by Radisky et al. [31]. The pMETYFH yeast strain had the knockout of the *YHF1* gene and carried an exogenous *YFH1* gene under the control of a methionine dependent promoter. This strain has a tightly regulated expression of frataxin with the ability to repress its expression in 2 h by the addition of methionine to the

medium. Regulation of the inducible *YHF1* had a direct effect on the *FET3* gene, a component of the high affinity iron uptake system of the plasma membrane. Repression of *YFH1* induced up-regulation of *FET3*, which resulted in increased uptake of iron by the cell followed by iron accumulation in mitochondria. Expression of the frataxin homologue, instead, induced a decrease in *FET3* expression. The authors suggested that the accumulation effect was not the result of an increase in iron uptake by the mitochondria but was caused by a reduction of efflux, the process that export iron out of the mitochondria. Taken together, these data seemed to point to a role of Yfh1 as a regulator of mitochondrial iron homeostasis. The researchers concluded that mitochondrial damage associated with *YFH1* repression was caused by an iron dependent increase in oxidative stress [31]. Ten years later, Moreno et al. [28] developed a refined inducible yeast model by modifying the promoter of the endogenous *YFH1* gene with a TetO promoter [28]. This system allowed the authors to repress Yfh1 expression by adding doxycycline to the medium. The temporal relationship of different phenotypes was followed more accurately by analysing the effect of *YFH1* repression at several time points throughout a 72 h window. The researchers found that iron accumulation in mitochondria was the first phenotype to appear (14 h) followed by decrease of aconitase and its activity. Following the respiratory chain (complexes I and III) which are part of another metabolic pathway strictly associated with iron-sulfur cluster proteins, the authors found that the oxygen consumption rate, a measure of the respiratory chain activity, started to decrease only after iron accumulation. The expression levels of *FET3* were found to be similar to those observed by Radisky et al. [28, 31]. In agreement with previous studies in which reduction of superoxide dismutase (SOD) activity in Δ*YFH1* cells [32, 33] and increase in carbonylated proteins [34], protein carbonylation was detected by Moreno et al. but only 24 h after repression of *YFH1*, clearly after the detection of iron deposits and more or less at the same time as the reduction in aconitase activity [28]. SOD activity showed a steady decrease with significant decline after 24 h. These results all pointed towards an iron dependent increase in ROS that affects iron-sulfur cluster containing proteins. Aconitase activity in *YFH1* cells could be preserved only under strict anaerobic conditions [34] indicating a correlation between its reduction and ROS rather than a link to reduced iron-sulfur cluster biogenesis. This model was used to show a correlation between disruption of iron homeostasis and the metabolic reprogramming that induces reduction in iron-sulfur cluster biogenesis [35].

**Drosophila models**

Navarro et al. produced in 2010 a Drosophila model based on RNA interference that showed accumulation of lipid droplets in glial cells, lipid peroxidation, increased susceptibility to oxidative stress, neurodegeneration and reduced life span [36]. The researchers concluded that lipid accumulation was due either to an increase in synthesis or to reduction in lipid catabolism. Some of the detected phenotypes were ameliorated by overexpression of the ApoD homologue *GLaz*, a protein involved in the lipid metabolism that has a role in oxidative stress defences of fly cells. Accumulation of lipid droplets was one of the main phenotypes detected in a second Drosophila model developed by Chen et al. in 2016 [29]. This model was based on a mosaic mutant with *fh* photoreceptor neurons. Young flies showed an expansion of the endoplasmatic reticulum and accumulation of lipid droplets while degeneration of the photoreceptor was subsequently detected in older flies. It was also observed that the mitochondria had abnormal morphology, complex I was compromised and ATP production severely reduced. *Fh* knockout was strongly associated with iron accumulation in mitochondria but, as opposed to the results found by Navarro et al., the researchers were unable to detect any increase in oxidative stress and overexpression of the ROS scavengers SOD1 and SOD2 did not reduce neurodegeneration indicating a ROS-independent mechanism. The researchers suggested a connection between iron accumulation and increased sphingolipid synthesis that in turn activates Pdk1, a kinase, and Mef2, a transcription factor associated with muscle differentiation, leading to neurodegeneration [29]. A ROS-independent neurodegeneration mechanism in Drosophila [37, 38] was not supported by all models. Increased sensitivity to $H_2O_2$ was shown in an RNA interference model [39]. Interestingly, mortality in flies was rescued by overexpression of CAT, a peroxisomal catalase with ROS protective properties, but not by overexpression of SOD1 and SOD2 [39]. Treatments with antioxidant idebenone or rapamycin were also shown to produce a protective effect against oxidative stress in two additional Drosophila models [40, 41]. The role of oxidative stress in an RNA interference Drosophila model was also shown in a different study in which it was shown that downregulation of *fh* and hyperoxia conditions greatly affect aconitase activity and reduce the life span of flies [42]. Reduction of aconitase activity was only detected when the flies where subjected to hyperoxia condition suggesting a protective role of FH against oxidative stress. On the other hand, increased oxidative stress did not affect the activity of succinate dehydrogenase suggesting that this effect does not extend to all iron-sulfur cluster enzymes [42].

**Mice models**

One of the very first models of FRDA was developed in mouse leading to complete knockout. This resulted in embryonal death demonstrating how essential the *FXN* gene is [43]. Later on Ristow and colleagues developed a mouse cell model in which they induced frataxin overexpression and saw a calcium-induced upregulation of the tricarboxylic acid cycle flux and respiration, which resulted in an overall increase of the cellular ATP levels. These results suggested that a role of frataxin in mitochondrial energy conversion and oxidative phosphorylation but said little about the temporal appearance of oxidative stress [44]. Chen et al. developed a knockout *Fxn* mouse model using CRISPR/Cas9 in an attempt to reproduce the results obtained in their Drosophila model. The gene editing molecules were delivered to the brain of young mice via AVV particles [45]. The knockout mice showed a phenotype similar to a previous mouse model [46] with shorter life span, neurological damage and altered sphingolipid synthesis. Iron levels in the cortex were increased and the PDK1 and Mef2 genes were up-regulated. As previously reported in their fly model, Chen et al. could not detect increase in oxidative stress (lipid peroxidation) [45]. The two Chen models in Drosophila and mouse agree also with data obtained from FRDA patients' samples where PDK1 and sphingolipids were found to be increased. These results point towards the same conclusions indicating consistency between different organisms. Abnormal lipid metabolism was detected also in a liver knockout mouse model in the form of accumulated lipid droplets [47]. This phenotype was detected at an early stage (4 weeks) and was associated with abnormal mitochondria, iron-sulfur cluster biogenesis disruption and, in some cases, with electron-dense structures typical of iron deposits. As for the model by Chen et al., another mouse model (Frda/MCK mouse) suggested an oxidative stress-independent mechanism [48, 49]. The primary phenotype identified by Seznec et al. was a decrease in iron-sulfur cluster enzymes activity only later followed by iron accumulation. Oxidative stress seemed not to be part of the pathophysiology and, accordingly, approaches to increase antioxidant defences had no effects [48]. Disruption of iron-sulfur cluster biogenesis, oxidative stress and iron accumulation are all phenotypes associated with FRDA but results obtained from different mouse models do not always agree on their presence and relationship. A Cre/Lox inducible *Fxn* knockout model based on murine fibroblasts was recently used to address these discrepancies and, more importantly the temporal relationship between different phenotypes [30]. The earliest event identified was a 14% reduction in aconitase activity followed by a decrease in ATP production and oxygen consumption. Oxidative stress, identified as an increase in ROS, was identified only after iron-sulfur cluster disruption

and iron accumulation was observed only as a late event [30]. Conditional *Fxn* KO was not the only approach used to create a FRDA mouse model. A successful approach was based on the introduction of a human FXN gene construct in *Fxn* null mice. The exogenous human gene, derived from FRDA patients, is usually characterised by the presence of a GAA expansion in the first intron that has all the characteristics of the original FRDA-causing mutation. Several iterations of this model were suggested based on different GAA expansion lengths [50, 51]. Characterisation of the YG8 and YG8sR models, carrying FXN exogenous genes with 190+90 or 200 GAA repeats, respectively, showed age dependent FRDA symptoms such as ambulatory difficulties, decreased frataxin mRNA levels, abnormal root ganglia, reduced aconitase activity and oxidative stress [50, 51]. These models, in addition to recapitulating the characteristic FRDA phenotype, were also well suited to study the genetic aspects of the disease such as GAA repeat instability [52], gene silencing induced by the expansion [53] and novel gene therapy approaches [54, 55].

**A human cell model**

In 2015, we developed a CRISPR-based system and engineered a cell line based on immortalized Human Embryonic Kidney cells HEK293 in which an exogenous inducible *FXN* (iFXN) gene rescues the cells from biallelic knockout of the endogenous *FXN* genes [56]. Even though this line is not optimal to recapitulate the tissues mainly affected in FRDA patients it was a convenient choice to establish the proof of principle of the approach in the first instance. The specific CRISPR used was chosen to have the required proximity of its target sequence to exon 4 of *FXN*. We obtained a targeting construct (pFSVpur-LoxP-TCI4) which, when integrated by homologous recombination, was able to excise exon 4 completely and replace it with a puromycin resistance cassette. We then produced knockout of both FXN alleles which required two rounds of transfection with CRISPR-I4 and the targeting construct because simultaneous homozygous FXN knockout is a rare event. The presence of the puromycin cassette flanked by two Lox-P sites allowed us to select the targeted cells in the first round followed by Cre recombinase-mediated excision of the puromycin cassette and a second round of targeting using the same pFSVpur-LoxP-TC-I4 construct. The targeting experiments carried out with CRISPR-I4 and pFSVpur-LoxP-TC-I4 showed a targeting frequency of ~50% to be compared to a 0% frequency when cells were transfected with only pFSVpur-LoxP-TC-I4 targeting construct. This step therefore proved the feasibility of successfully performing gene editing at the *FXN* locus. The inducible iFXN cassette allowed

us to modulate the amount of frataxin in the cell by over or under– expression of the gene itself. This system has allowed us not only to gain insights in the disease mechanism (under-expression) but also to obtain useful information on the effects of FXN concentration on several mitochondrial pathways (over-expression) using a number of traditional and new biomarkers that detect cellular ROS, with indicators of iron-sulfur cluster formation such as aconitase levels which has successfully been used in other FRDA studies [57]. We discuss the different approaches in the following paragraph. In the future, we plan to develop a new cellular model that mimics more faithfully the tissues affected by FRDA based on inducible Pluripotent Stem (iPS) cells. These cells have the advantage of differentiating in FRDA-relevant cell types like sensory neurons and cardiomyocytes and of having a normal karyotype (normal diploid, normal XY).

**New Methodologies to the study of oxidative stress**

Most of the early studies of FRDA used the activity of aconitase and other mitochondrial enzymes as a parameter to follow the phenotype. This important parameter may however be insufficient to accurately describe disease progression. More recently other markers have been followed. The development of new fluorescent probes can allow a sensitive quantification of ROS. The introduction on the market of the Seahorse XF technology (Mito stress test, Agilent) has allowed direct measurement of the Oxygen Consumption Rate (OCR) in living cells, a parameter very important to understand the degree of cellular stress [58]. In association with three different compounds (oligomycin, FCCP and a mixture of rotenone/ antimycin A) that are sequentially added to the medium, the measured variation in OCR can be used to assess simultaneously the state of several mitochondrial functions like basal respiration, ATP production, maximal respiration and non-mitochondrial respiration. Another technique which we recently developed for the study of FRDA is *in cell* infrared absorption spectroscopy, which provide valuable information on the structure content of cellular components associated with Correlated Cellular Microscopy (CSM) analysis. CSM relies on Two-Dimensional Correlation Spectroscopy (2DCOS) [59] to assign complex band patterns in cellular spectra that co-evolve over time, based on the correlation of their changes and clustering together the bands that evolve in synchrony. Finally, we recently demonstrated that a novel biosensor, the nanomotion sensor, can be used to perform real-time, correlated measurements of different cellular nanoscale biomotions and metabolic activities, while stimulating the cells with physical or chemical stimuli [60]. This innovative method combines conventional bio-investigation techniques and custom analysis chambers [61] with

a nanomechanical oscillator, typically an atomic force microscopy cantilever, to obtain a device that can transduce the smallest cellular motion or vibration in measurable signals [62]. The resulting electrical signal yields real-time information on the metabolic state of cells incubated on the cantilever in the analysis chamber. Together these new techniques could in the future provide new and complementary information and help us to reconstruct the disease progression of FRDA.

**Towards a cure**

In principle, to cure FRDA various alternatives have been considered: a) increase the expression of the *FXN* gene, b) interfere with the proteasomal degradation of frataxin or c) remove the anomalous expansion of the GAA-TTC tandem repeat from the *FXN* gene. Many efforts have been made to improve the *FXN* gene expression. The most efficient strategy involves the interference with the *FXN* gene silencing. It has been found that the suitable amount of frataxin is produced by a complex interplay of activators and repressors operating on the gene. Among the repressors, a prominent role has been found for 2-aminobenzamide class of histone deacetylase (HDAC) repressors [63]. However, this strategy appears to be risky as the HDAC inhibitors show marked toxicity [64]. Reduction of the anomalous expansion of the GAA-TTC tandem repeat to the physiologic 50, seems to be the most promising alternative to fight FRDA.

**Conclusions**

In conclusion, we have discussed how FRDA can be considered as a prototypical example of the problems and solutions proposed by a disease associated to ROS increase and oxidative stress. We believe that most of the methodologies developed for FRDA can be applied also to other diseases and will allow us in the future to better place the role of oxidative stress in disease.

**Acknowledgements**

The research described from AP lab was supported by MRC (U117584256).

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**Table 1 –** Summary of the phenotypes observed in the current animal models as discussed in the text.

| Animal models | Cellular phenotypes | Ref. |
|---|---|---|
| Yeast models | Mitochondrial iron accumulation, oxidative stress, decreased Fe-S enzymes activity and oxygen consumption rate reduction | [28, 31-34] |
| Drosophila models | Altered lipid synthesis with accumulation of lipid droplets, mitochondrial iron accumulation, decreased Fe-S enzymes activity, oxidative stress*, decreased ATP production. | [29, 36, 39-42] |
| Mouse models | Altered lipid synthesis, mitochondrial iron accumulation, decreased Fe-S enzymes activity, oxidative stress** | [30, 45-49, 51] |

* Found in most models except in [29]

** Found in [30, 51]

**Figure 1** – The structure of frataxins. A) ribbon representation of human frataxin (1ekg). The side chains of the residues of the exposed negatively charged ridge are explicitly shown. B) and C) Backbone and space filling representations of the complex of bacterial frataxin (CyaY) with the two central components of the iron-sulfur cluster biogenesis, IscS and IscU [22].

Figure 1

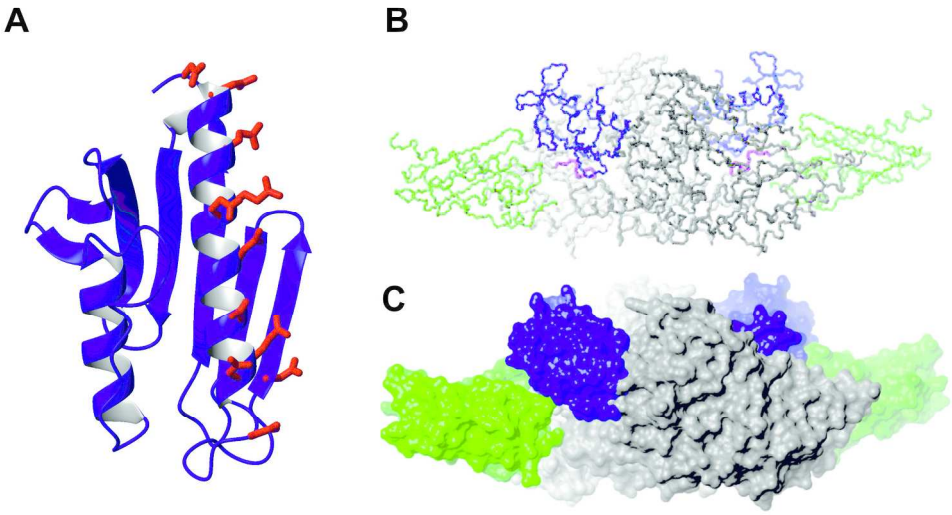


Figure 1

187x115mm (300 x 300 DPI)