Chapter 37

Mitochondrial Dysfunction in Friedreich Ataxia

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Abbreviations*:* FRDA, Ataxia di Friedreich; FXN, frataxin; DRG, dorsal root ganglia; LOFA, late onset Friedreich ataxia; MRI, magnetic resonance imaging; MPP, Mitochondrial processing peptidase; ISC, iron sulphur cluster; Fe, iron; S, sulphur; ETC, electron transport chain; NADH, Nicotinamide adenine dinucleotide; ROS, reactive oxygen species; CGNs, cerebellar granule neurons; dPUFAs, poly-unsaturated fatty acids; GSH, reduce glutathione; IMM, inner mitochondrial membrane; Nrf2 Nuclear factor (erythroid-derived 2)-like 2; SERCA, sarcolemmal ATPase RyR2, ryanodine receptors; MCU, mitochondrial calcium uniporter 1.

Abstract

Friedreich's Ataxia (FRDA) is the commonest hereditary form of ataxia affecting the Western European population. FRDA is an autosomal recessive neurodegenerative disorder caused by an intronic GAA repeat expansion within the *FXN* gene; the 96% of the patients are homozygous, while the remaining 4% are compound heterozygous carrying the GAA repeat mutation on one allele and point mutations on the other one.Usually FRDA first symptoms appear at young age during the firsts two decades of life. The clinical features include progressive gait and limb ataxia, dysarthria, muscle weakness, peripheral sensory neuropathy, pes cavus, and scoliosis. FRDA is a multi-systemic disorder; therefore, patients develop non-neurological signs, such as hypertrophic cardiomyopathy, diabetes, and urological problems.

The genetic mutation leads to a progressive decrease of the mitochondrial protein frataxin, which resides in the inner mitochondrial membrane. Frataxin is a small essential protein of 210 amino acids whose structure in the C-terminal region is conserved in all organisms from bacteria to

human. Mitochondrial dysfunction in FRDA is strictly linked to frataxin functional role in the iron biogenesis. Frataxin deficiency leads to impairment ISCs formation which in turn affects the ISC-containing proteins (including complex I, II, and III of the mitochondrial electron transport chain and aconitase). The pathogenic mechanism triggered by the reduced production of frataxin leads to the generation of oxidative stress, mitochondrial energy imbalance and an increase in lipid peroxidation, as shown in cerebellar granule neurons (CGNs), and mouse fibroblasts. Lipid peroxidation has been proven to be one of the causes inducing neuronal death, as by pre-treating the cells with poly-unsaturated fatty acids (dPUFAs), the phenotype was rescued. In this chapter we review the current knowledge on the mitochondrial dysfunction in FRDA.

Key words: FRDA, GAA repeats, FXN, frataxin, mitochondrial dysfunction, neurodegeneration cardiomyopathy.

1. Pathogenesis of Friedreich's Ataxia

Friedreich's Ataxia (FRDA) is the commonest hereditary form of ataxia affecting the Western European population (Pandolfo, 2008). At the end of the 19th century, Nikolaus Friedreich described its pathology for the first time. More than one hundred fifty years after the discovery, we know more about the genetic origin and the pathological features. However, the pharmacological intervention for this disorder remains elusive (Schulz and Pandolfo, 2013).

FRDA is an autosomal recessive neurodegenerative disorder caused by an intronic GAA repeat expansion within the *FXN* gene, and the 96% of the patients are homozygous, while the remaining 4% are compound heterozygous carrying the GAA repeat mutation on one allele and point mutations on the other one (Campuzzano et al., 1996; Gellera et al., 2007). The pathology affects the Caucasian population independent of gender, and rarely affects Southeast Asian and African individuals (Delatycki and Corben, 2013).

Expanded GAA repeats may vary in length during disease progression by a process called somatic instability, which usually starts during the embryonic stage and continues along life with an elongation of the repeat expansion (De Biase et al., 2007; Long et al., 2017). Usually GAA repeat expansions have been characterized in terms of the overall repeat size, and inversely correlate with the age at onset. However the variability is high therefore studies to investigate modifiers are warrant. It has been seen in another triplet repeat disorder SCA1 that interruption in the expanded CAG repeat was a relevant modifier of the phenotype (Menon et al., 2013). Therefore Al-Mahdawi et al., 2018 studied DNA samples from 238 FRDA patients and 7 carriers using long-rate PCR and the restriction enzyme MboII, showing that only in few cases a large interruptions in GAA

expansions was presentThey concluded that small interruptions may be related with FRDA disease phenotype, similar to other genetic disorders (Menon et al., 2013).

The *FXN* gene is located in the chromosome 9q13 and the mutation impedes its transcription (Grabczyk and Usdin, 2000), reducing the level of downstream frataxin (FXN) protein in the cells. FXN is a mitochondrial protein located in the inner mitochondrial membrane and causing iron biogenesis deficiency. The range of GAA repeat expansion can span between 70 and 1700, however, the average patients have been shown to have around 600 and 900 repeats (Pandolfo, 2001).

Typically, the first symptoms of FRDA appear at young age during the firsts two decade of life. However, there are also late onset and very late onset cases. The time of onset depends on the length of the shorter GAA expanded allele; the longer are the expansions the earlier is the onset of the symptoms (Filla et al., 1996; Mateo et al., 2004). The diagnosis is confirmed using genetic techniques that reveal the length of the repeat expansion.

2. Clinical Features

FRDA is characterized by progressive neurodegeneration of DRG and cerebellar atrophy. Patients also develop axonal neuropathy and in a later stage of the diseases loss of the myelination (Hughes et al., 1968; Koeppen et al., 2009). The clinical features include progressive gait and limb ataxia, dysarthria, muscle weakness, lack balance and coordination, peripheral sensory neuropathy, skeletal abnormalities such as pes cavus or equinovarus deformity of the feet and scoliosis, loss of joint position, or vibration sense (Harding, 1981; Delatycki and Corben, 2013; Parkinson et al., 2013). Cognitive function may also be affected (Mantovan et al., 2006), although concrete thinking is present; some patients lack of verbal fluency, motor, and reaction times (Corben et al., 2006; Nieto et al., 2012). FRDA is a multi-systemic disorder; therefore, patients develop non-neurological signs, such as hypertrophic cardiomyopathy, diabetes and urological problems.

Among the above manifestations, cardiomyopathy affects around 85% of patients and may result in a premature death caused through heart failure (Casazza and Morpugno, 1996; Koeppen et al., 2015). Heart disease is commonly asymptomatic; however, some patients can present general symptoms of heart failure or palpitation (Payne et al., 2011). The commonest damage is hypertrophic cardiomyopathy, which can involve either the left ventricles or interventricular septum. At molecular level, it was found a clear iron accumulation (Sanchez-Casis et al., 1977) and mitochondrial dysfunction linked to calcium dyshomeostasis (Abeti et al., 2018b).

Another clinical symptom of FRDA is diabetes mellitus that occurs in 5%–40% of the cases (McCormick et al., 2017). The mechanism by which diabetes occurs is not well understood but may be associated to an insulin resistance of peripheral tissue and a decrease of insulin secretion from β-pancreatic cells (Finocchiaro et al., 1988), probably related to a mitochondrial dysfunction (MD).

3. The Frataxin Protein and the Mitochondrial Dysfunction

The genetic mutation leads to a progressive decrease of the mitochondrial protein frataxin, which resides in the inner mitochondrial membrane. Frataxin is a small essential protein of 210 amino acids whose structure in the C-terminal region is conserved in all organisms from bacteria to human (Adinolfi et al., 2002).

After transduction, the protein translocates into the mitochondrial membrane for two proteolytic steps. Mitochondrial processing peptidase (MPP) first cleaves the 23kDa precursor to intermediate between Gly41 and Leu42 residues. Then MPP by a second proteolytic cleavage between Lys80 and Ser81 converts the intermediate of 19 kDa to yield mature frataxin (frataxin (81–210) which is the predominant form (Kouticova et al., 1998; Schmucker et al., 2008) and the mature form is a 14.2 kDa mitochondrial protein. Frataxin is ubiquitously expressed, but the highest levels are found in tissues with high-energy demand, such as the nervous system, heart and liver.

Mitochondrial dysfunction in FRDA is strictly linked to frataxin functional role in the iron biogenesis (Stemmler et al., 2010). Frataxin deficiency leads to impaired ISCs formation which in turn affect the ISC-containing proteins (including complex I, II, and III of the mitochondrial electron transport chain and aconitase) (Pastore and Puccio, 2013).

Importantly the FXN protein controls an important step of iron mitochondrial uptake. This happens between the iron transported by mitoferrin 1 and mitoferrin 2 and the inorganic sulphide to form a transient Fe-S on the ISCU scaffold protein (Ferecatu et al., 2014). Amongst the possible physiological functions of the frataxin, it was found that it acts as a ferritin-like scavenger to control the iron availability (Adinolfi et al., 2002). In addition, a high affinity was found between the frataxin and the ferrochetalase suggesting an involvement of the protein into the heme group synthases (Lesuisse et al., 2003).

Puccio and colleagues found that cardiomyopathy in FRDA is associated to the ISCs formation through lack of frataxin (Puccio et al., 2001). The first investigation hypothesized that frataxin was the iron donor during the ISCs biogenesis (Yoon and Cowan, 2003) but later Adinolfi and colleagues found that the role of frataxin is also associated to the iron transport (Adinolfi et al., 2009). Additionally, different studies showed that frataxin is linked to the electron transport chain (ETC) complex within the mitochondria, in particular to complex I, II, and III. Although, few

proteins might be inhibited by the reduced level of ISCs, Abeti and colleagues were able to identify that Complex I was prevalently defective in cellular models of FRDA (Abeti et al., 2016, 2018b). The reason for this given is the fact that Complex I requires more ISCs than other complexes. Experiments conducted on the NADH redox state and pool revealed that Complex I was inhibited and that there was a lack of substrate (Abeti et al., 2018b).

Mitochondria are the sites where the cell produces energy and generates reactive oxygen species (ROS) (Nickel et al., 2014). Increased level of free radicals in cells seriously damage proteins, lipids and nucleic acids. The pathogenic mechanism triggered by the reduced production of frataxin leads to the generation of oxidative stress, mitochondrial energy imbalance and an increase in lipid peroxidation, as shown in cerebellar granule neurons (CGNs), and mouse fibroblasts – see Figure 1 (Abeti et al., 2015, 2016).

Lipid peroxidation has been proven to be one of the causes of inducing neuronal deathin FRDA cell models, as by pre-treating the cells with poly-unsaturated fatty acids (dPUFAs), the phenotype was rescued (Abeti et al., 2016). Another marker of pathophysiology was the deemed level of reduced glutathione (GSH) (Abeti et al., 2016, 2018a).

Figure 1. Description of the predicted molecular pathophysiology in FRDA neurons. Genetic mutation within the *FXN* gene impedes the transcription and causes a decrease frataxin, a mitochondrial protein located on the inner mitochondrial membrane (IMM) which serves iron biogenesis. Frataxin deficiency results in iron accumulation, oxidative stress and mitochondrial dysfunction.

Amongst the therapeutic strategies applied to FRDA, over the years, antioxidants have been shown to have a positive outcome (Cooper and Schapira, 2007; Cooper et al., 2008). However, due to lack of natural history, these studies did not proceed to final conclusion.

In human fibroblasts from patients a marked sensitivity was found to pro-oxidant agents (Paupe et al., 2009; Shan et al., 2013), which was due to the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) failure to translocate from cytosol to nucleus (Paupe et al., 2009). Recently, we demonstrated that Omav (which specifically triggers the Nrf2 pathway) had a beneficial effect on oxidative stress and mitochondrial dysfunction in FRDA models (Creelan et al., 2017; Abeti et al., 2018a). The turnover of Nrf2 is regulated through ubiquitination where Omav operates; pre-treating the cells with this compound the oxidative stress was reduced and the cell survival was promoted (Abeti et al., 2016, 2018a). Importantly Nrf2 is also involved in mitochondrial biogenesis; indeed, Hayashi and colleagues found a reduced mtDNA copy number in knockout Nrf2 mice (Hayashi et al., 2017).

The studies on oxidative stress and MD were important to characterize the physiological function of frataxin, which could also be involved indirectly in calcium (Ca^{2+}) homeostasis. A novel study highlighted that in FRDA-like cells the Ca^{2+} level in the stores was altered (Abeti et al., 2018b). By investigating the Ca^{2+} homeostasis the authors found that both FRDA-like neurons and cardiomyocytes have a decreased ER/SR Ca^{2+} content. Neurons were unable to go back to resting state after plasma membrane depolarization, suggesting a probable defect on the sarcolemmal ATPase (SERCA), while cardiomyocytes revealed that the reduced Ca^{2+} content was due to an over activity of ryanodine receptors (RyR2s). Moreover, it was found that mitochondrial also inhibited Ca^{2+} uptake, similarly to other FRDA-like models (Bolinches-Amorós et al., 2014) and that Vitamin E, a lipophilic antioxidant, restored the signal and prevented apoptosis induced by Hypoxia Reperfusion (Abeti et al., 2018b).

4. Conclusion

From clinical features to molecular abnormalities, in this chapter, we summarized the current knowledge of FRDA.. The progressive silencing of FXN leads to mitochondrial energy imbalance causing alterations within specific tissues. We have demontrated that Complex I inhibition and lipid peroxidation play an important role in the pathogenesis of the mitochondria pathology in FRDA. Although we have made substantial progresses in understanding the role of the mitochondrial protein, frataxin, further investigations are essential to develop novel therapeutic strategies.

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