Molecular and Cellular Neuroscience 55 (2013) 50–61

Contents lists available at SciVerse ScienceDirect

Molecular and Cellular Neuroscience

journal homepage: www.elsevier.com/locate/ymcne

Iron–sulfur cluster synthesis, iron homeostasis and oxidative stress in Friedreich ataxia

Rachael A. Vaubel, Grazia Isaya *

Departments of Pediatric & Adolescent Medicine and Biochemistry & Molecular Biology and the Mayo Clinic Children's Center, Mayo Clinic, Rochester, MN 55905, USA

ARTICLE INFO

Article history:
Received 23 April 2012
Accepted 5 August 2012
Available online 11 August 2012

Keywords:
Friedreich ataxia
Frataxin
Mitochondria
Iron–sulfur clusters
Heme
Oxidative stress
Anti-oxidants
Iron-chelators

ABSTRACT

Friedreich ataxia (FRDA) is an autosomal recessive, multi-systemic degenerative disease that results from reduced synthesis of the mitochondrial protein frataxin. Frataxin has been intensely studied since its deficiency was linked to FRDA in 1996. The defining properties of frataxin – (i) the ability to bind iron, (ii) the ability to interact with, and donate iron to, other iron-binding proteins, and (iii) the ability to oligomerize, store iron and control iron redox chemistry – have been extensively characterized with different frataxin orthologs and their interacting protein partners. This very large body of biochemical and structural data [reviewed in (Bencze et al., 2006)] supports equally extensive biological evidence that frataxin is critical for mitochondrial iron metabolism and overall cellular iron homeostasis and antioxidant protection [reviewed in (Wilson, 2006)]. However, the precise biological role of frataxin remains a matter of debate. Here, we review seminal and recent data that strongly link frataxin to the synthesis of iron–sulfur cluster cofactors (ISC), as well as controversial data that nevertheless link frataxin to additional iron-related processes. Finally, we discuss how defects in ISC synthesis could be a major (although likely not unique) contributor to the pathophysiology of FRDA via (i) loss of ISC-dependent enzymes, (ii) mitochondrial and cellular iron dysregulation, and (iii) enhanced iron-mediated oxidative stress. This article is part of a Special Issue entitled 'Mitochondrial function and dysfunction in neurodegeneration'.

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Introduction

Friedreich ataxia (FRDA; OMIM number 229300) is the most common genetically inherited ataxia with an estimated incidence of 1:40,000 [for recent reviews of FRDA clinical and pathological aspects see (Koeppen, 2011; Pandolfo, 2009)]. Patients are largely asymptomatic during the first 5–10 years of life until they develop a progressive loss of movement coordination and other deficits, including cardiac disease, muscle weakness, skeletal deformities, vision and hearing impairment, and diabetes. Often as young as teenagers, patients become wheelchair-bound and unable to perform daily activities independently, with cardiac failure representing a frequent cause of death as early as the second decade of life. The majority of patients carry intronic GAA triplet repeat expansions that cause transcriptional silencing of the FRDA gene via different mechanisms [reviewed in (Gottesfeld, 2007; Wells, 2008)], ultimately leading to reduced levels of frataxin, a mitochondrial protein encoded by the FRDA gene (Campuzano et al., 1996). Although frataxin is ubiquitously expressed (Campuzano et al., 1997), frataxin deficiency affects primarily certain regions of the central and peripheral nervous systems as well as the heart, skeleton, and endocrine pancreas, which accounts for the major clinical and pathological aspects of FRDA (Koeppen, 2011). The underlying factors responsible for this tissue-specific susceptibility remain undefined. Currently, there is no cure for FRDA but several therapeutics are in preclinical or clinical development [reviewed in (Wilson, 2012)].

Deficient ISC synthesis and the pathophysiology of FRDA

ISC are essential and highly adaptable enzyme co-factors that can participate in a wide range of cellular reactions and processes [reviewed in (Johnson et al., 2005)]. In eukaryotic cells, ISC-containing enzymes have been identified in the mitochondria (*e.g.* Kreb's cycle and electron transport chain), the cytoplasm (*e.g.* ribosome biogenesis), and the nucleus (*e.g.* DNA synthesis and repair mechanisms) [reviewed in (Lill et al., 2012; Ye and Rouault, 2010)]. Yeast and animal cells synthesize ISC primarily in the mitochondrial matrix (Lill et al., 2012; Muhlenhoff et al., 2002; Schilke et al., 1999), while ISC synthesis in other cellular compartments depends on as yet undefined factors or signals that are available only when ISC synthesis is functional in the mitochondria (Gerber et al., 2004; Kispal et al., 1999; Lill et al., 2012; Martelli et al., 2007; Pondarre et al., 2006; Ye and Rouault, 2010). In addition, it is well established that defects in mitochondrial ISC synthesis are associated with a rapid increase in cellular iron uptake and a re-distribution of iron

Abbreviations: ISC, iron–sulfur clusters; FRDA, Friedreich ataxia; NFS1/Nfs1, human/yeast cysteine desulfurase; ISD11/Isd11, human/yeast NFS1-/Nfs1-binding protein; ISCU/Isu1, human/yeast scaffold protein; MPP, mitochondrial processing peptidase.

* Corresponding author at: Mayo Clinic, 200 First Street SW, Stabile 7-52, Rochester, MN 55905, USA. Fax: +1 507 266 9315.
E-mail address: isaya@mayo.edu (G. Isaya).

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doi:10.1016/j.mcn.2012.08.003

within the cell, leading to mitochondrial iron accumulation and cytoplasmic iron depletion (Babcock et al., 1997; Chen et al., 2004; Knight et al., 1998; Li et al., 1999; Whitnall et al., 2008) [reviewed in (Rouault and Tong, 2005)]. Thus, mitochondrial ISC synthesis is key to the maintenance of numerous vital enzymatic activities as well as the maintenance of cellular iron homeostasis. Not surprisingly, a complete loss of mitochondrial ISC synthesis is incompatible with life (Cossee et al., 2000; Kispal et al., 2005; Lill and Kispal, 2000). Moreover, even partial defects in mitochondrial ISC synthesis can lead to severe phenotypes typically dominated by mitochondrial abnormalities, including impaired energy metabolism, oxidative damage and loss of mitochondrial DNA integrity (Karthikeyan et al., 2003; Knight et al., 1998; Li et al., 1999). Concomitant extra-mitochondrial abnormalities include multiple ISC-containing enzyme deficiencies that lead to nuclear genome instability (Veatch et al., 2009), impaired ribosome biogenesis (Kispal et al., 2005), impaired amino acid metabolism (Kispal et al., 1999), and other effects [reviewed in (Ye and Rouault, 2010)].

The pathophysiology of FRDA was linked to defects in ISC synthesis early on, when Rustin and Colleagues first reported a deficient activity of the ISC-containing subunits of mitochondrial respiratory complexes I, II and III in the endomyocardial biopsy of two FRDA patients (Rotig et al., 1997). Mitochondrial aconitase, a [4Fe–4S] enzyme in the Kreb's cycle, was also found deficient. Similar multiple ISC-dependent enzyme deficiencies were observed upon deletion of the *YFH1* gene (encoding the yeast frataxin homolog, Yfh1) in *Saccharomyces cerevisiae* (Foury, 1999; Rotig et al., 1997). Subsequent studies showed that the lack of human or mouse frataxin caused early defects in ISC-dependent enzymes, which preceded other mitochondrial alterations such as mitochondrial iron accumulation (Puccio et al., 2001; Stehling et al., 2004). Since these initial studies, eukaryotic frataxin orthologs have been universally shown to stimulate ISC synthesis *in vitro* (Cook et al., 2010; Gakh et al., 2010; Li et al., 2009; Tsai and Barondeau, 2010; Yoon and Cowan, 2003) [prokaryotic frataxin was recently shown to inhibit ISC synthesis under certain conditions (Adinolfi et al., 2009) that will be discussed later]. Thus, a large body of data supports early and recent proposals that the complex phenotypes associated with frataxin deficiency in humans and other eukaryotes reflect at least in part an impaired ability to synthesize ISC (Foury, 1999; Pandolfo, 2006; Rotig et al., 1997; Wilson, 2006). Indeed, frataxin depletion is consistently associated with multiple ISC enzyme deficiencies in mitochondria and throughout the cell (Foury, 1999; Martelli et al., 2007). These deficiencies are accompanied by global dysregulation of cellular iron homeostasis that leads to mitochondrial iron accumulation and cytosolic iron depletion (Babcock et al., 1997; Foury and Cazzalini, 1997; Huang et al., 2009; Whitnall et al., 2008). Although mitochondrial iron accumulation is inconsistently observed in FRDA cell lines (Delatycki et al., 1999; Wong et al., 1999), the state of mitochondrial iron in these cells is clearly altered independent of a net increase in mitochondrial iron content (Wong et al., 1999). Similarly, total iron content was not significantly higher in the left ventricle of FRDA patients compared to controls (Michael et al., 2006), however, iron deposits were observed inside FRDA cardiomyocytes (Koeppen, 2011; Lamarche et al., 1980; Michael et al., 2006) and electron-dense inclusions inside the mitochondria of those cardiomyocytes, which appeared to result from accumulation of iron-loaded mitochondrial ferritin (Koeppen, 2011). Furthermore, total iron content was not significantly increased in FRDA dorsal root ganglia, however, the presence of increased ferritin immunoreactivity in satellite cells of dorsal root ganglia neurons suggested regional iron accumulation and the possibility that both satellite cells and dorsal root ganglia neurons are affected by iron dysregulation in FRDA (Koeppen et al., 2009). Magnetic resonance imaging suggested iron accumulation in the nucleus dentatus of the cerebellum of young patients, indicating that iron dysregulation occurs early in FRDA in select regions of the nervous system (Boddaert et al., 2007; Velasco-Sanchez et al., 2011).

The mechanisms leading to mitochondrial iron dysregulation and regional iron accumulations in FRDA are complex. It is clear that the processes of mitochondrial iron accumulation and cytoplasmic iron depletion are linked to each other and are transcriptionally regulated (Chen et al., 2004; Foury and Talibi, 2001; Huang et al., 2009). Although the underlying signals are not completely understood, deficient ISC synthesis is a probable initiating event. In *S. cerevisiae*, mitochondrial iron accumulation is a hallmark of defects in ISC synthesis (Knight et al., 1998; Li et al., 1999). Similarly, the lack of human or mouse frataxin caused early defects in ISC enzymes prior to detectable mitochondrial iron accumulation (Puccio et al., 2001; Stehling et al., 2004). Moreover, frataxin depletion in mouse heart was associated with (i) global down-regulation of molecules involved not only in mitochondrial ISC synthesis but also iron storage and heme synthesis, and (ii) changes in the expression of molecules involved in cellular and mitochondrial iron uptake; these effects could synergistically contribute to mitochondrial iron accumulation in mammalian cells (Huang et al., 2009). While the accumulated iron is progressively converted to an oxidized and insoluble or ferritin-bound form (Knight et al., 1998; Koeppen, 2011; Seguin et al., 2010), studies in yeast and human cells indicate that iron dysregulation is an early effect of frataxin depletion, which increases the fraction of labile redox-active iron inside mitochondria (Karthikeyan et al., 2003; Wong et al., 1999). The combination of deficits in aconitase and respiratory chain activities with mitochondrial iron dysregulation is believed to result in progressive impairment of energy metabolism and accumulation of oxidative damage (Pandolfo, 2006; Wilson, 2006) (discussed extensively later). Importantly, in multicellular organisms these mitochondrial alterations in turn lead to changes in various cellular pathways involved in antioxidant, metabolic, and inflammatory responses, which most likely amplify the pathophysiology of FRDA and promote disease progression in susceptible tissues (Coppola et al., 2009; Lu et al., 2009; Paupe et al., 2009; Pianese et al., 2002; Sparaco et al., 2009; Wagner et al., 2012) [reviewed in (Pandolfo, 2012)].

The role of frataxin in iron–sulfur cluster synthesis

Mitochondrial ISC synthesis: from individual components to macromolecular machineries

The mitochondrial proteins known to be involved in ISC synthesis are highly conserved from yeast to humans, and many were actually inherited from bacteria (Fontecave and Ollagnier-de-Choudens, 2008). They include early components that provide the building blocks to assemble new [2Fe–2S] and [4Fe–4S] clusters (elemental iron and sulfur, and reducing equivalents), and late components that transfer these clusters to mitochondrial apo-proteins [reviewed in (Lill et al., 2012; Ye and Rouault, 2010)]. Additional components are thought to transport ISC precursors to the cytoplasm for the biogenesis of cytoplasmic and nuclear ISC-containing enzymes [reviewed in (Ye and Rouault, 2010)]. The general roles played by individual components have been assessed through genetic and biochemical studies in prokaryotes and *S. cerevisiae* and confirmed for the corresponding human components [reviewed in (Fontecave and Ollagnier-de-Choudens, 2008; Lill, 2009; Ye and Rouault, 2010)]. According to current models, synthesis of [2Fe–2S] clusters in the mitochondrial matrix is initiated on a scaffold protein (yeast Isu1/mammalian ISCU) and involves (i) a cysteine desulfurase (yeast Nfs1/mammalian NFS1, stabilized by a small binding partner, Isd11/ISD11) that serves as the sulfur donor; (ii) frataxin (yeast Yfh1/mammalian FXN) that serves as the iron donor; and (iii) the electron donor chain formed by ferredoxin reductase and ferredoxin (yeast Arh1-Yah1/mammalian FDXR-FDX2). Subsequently, release of ISC from Isu1/ISCU and their transfer to apo-enzymes are assisted by various chaperone and co-chaperones, proteins needed to reduce cysteine residues on apo-enzymes, and ISC carrier proteins (Lill et al., 2012; Ye and Rouault, 2010). In these models, the ISC scaffold protein, Isu1/ISCU, is thought to cycle between the early and the late components. However, recent studies indicate that ISC synthesis occurs on stable complexes built-up of at least four components: Nfs1, Isd11, Isu1 and Yfh1 in yeast; NFS1, ISD11,

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