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Review

The emerging role of iron dyshomeostasis in the mitochondrial decay of aging

Jinze Xu [a], Emanuele Marzetti [a,d], Arnold Y. Seo [a], Jae-Sung Kim [c], Tomas A. Prolla [e], Christiaan Leeuwenburgh [a,b,*]

[a] Department of Aging and Geriatrics Research, Division of Biology of Aging, Genomics, Metabolism and Biomarkers Core of the Institute on Aging, University of Florida, Gainesville, FL 32611, USA
[b] Department of Anatomy and Cell Biology, University of Florida, Gainesville, FL 32611, USA
[c] Department of Surgery, University of Florida, Gainesville, FL 32611, USA
[d] Department of Gerontology, Geriatrics and Physiatrics, Catholic University of the Sacred Heart, Rome 00168, Italy
[e] Department of Genetics and Medical Genetics, University of Wisconsin, Madison, WI 52706, USA

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ABSTRACT

Recent studies show that cellular and mitochondrial iron increases with age. Iron overload, especially in mitochondria, increases the availability of redox-active iron, which may be a causal factor in the extensive age-related biomolecular oxidative damage observed in aged organisms. Such damage is thought to play a major role in the pathogenesis of iron overload diseases and age-related pathologies. Indeed, recent findings of the beneficial effects of iron manipulation in life extension in *Caenorhabditis elegans*, *Drosophila* and transgenic mice have sparked a renewed interest in the potential role of iron in longevity. A substantial research effort now focuses on developing and testing safe pharmacologic interventions to combat iron dyshomeostasis in aging, acute injuries and in iron overload disorders.

1. Introduction

Iron is a trace metal essential for several life-sustaining functions, while excess iron, by virtue of its ability to catalyze the formation of reactive oxygen species (ROS), has the potential to be a causative factor in the age-related mitochondrial deterioration (Kohgo et al., 2008; Duvigneau et al., 2008; Liang et al., 2008). Iron accumulates in senescent cells and most non-hematopoietic tissues with age (Killilea et al., 2003, 2004; Dunaief, 2006; Hofer et al., 2008; Jung et al., 2008). Rapidly emerging evidence suggests that iron accumulation and loss of mitochondrial iron homeostasis may contribute to mitochondrial decay, which subsequently leads to aging (Table 1) (Bitar and Weiner, 1983; Atamna et al., 2001, 2002a; Napoli et al., 2006; Doulias et al., 2008; Seo et al., 2008; Xu et al., 2008; Irazusta et al., 2009; Cantu et al., 2009; Veatch et al., 2009; Chen et al., 2009). Although studies in both yeast and mammalian systems support the conclusion that iron homeostasis may be disrupted with age (Zacharski et al., 2000; Gau et al., 2001), the mechanisms underlying this phenomenon are still unclear. Here, we discuss important features of iron dyshomeostasis with a particular emphasis on its effects on mitochondrial decay and aging.

2. Iron crisis and mitochondrial decay

2.1. Labile iron in mitochondria

Iron taken up by eukaryotic cells must reach mitochondria, the unique site for heme and iron–sulfur cluster (ISC) biosynthesis (Dunn et al., 2007; Levi and Rovida, 2009). Since mitochondria are also the major source of intracellular ROS and excess iron has a strong catalytic potential to enhance ROS generation, it is important that mitochondrial iron concentration is maintained within a tightly controlled range. In cells and tissues, iron exists in two pools. Ferritin and iron-containing prosthetic groups in various proteins sequester "non-chelatable" iron that conventional iron chelators like deferoxamine are unable to chelate. The other iron pool is so-called "chelatable or labile" iron that represents both free and loosely bound iron. In hepatocytes, this labile iron is estimated to be about 5 μM (Ma et al., 2006). Most iron transferred from cytoplasm to mitochondria or delivered from late endosomes and lysosomes to mitochondria is sequestered efficiently by the iron storage proteins, frataxin and mitochondrial ferritin (MtF) (Scheme 1) (Kaur and Andersen, 2004; Zhang et al., 2005). With aging, a minor amount of mitochondrial iron, either loosely bound

* Corresponding author at: Division of Biology of Aging, Department of Aging and Geriatrics, Institute on Aging, College of Medicine, University of Florida, 210 East Mowry Road, PO Box 112610, Gainesville, FL 32611, USA. Tel.: +1 352 273 6796; fax: +1 352 273 5920.
E-mail addresses: cleeuwen@aging.ufl.edu, cleeuwen@ufl.edu (C. Leeuwenburgh).

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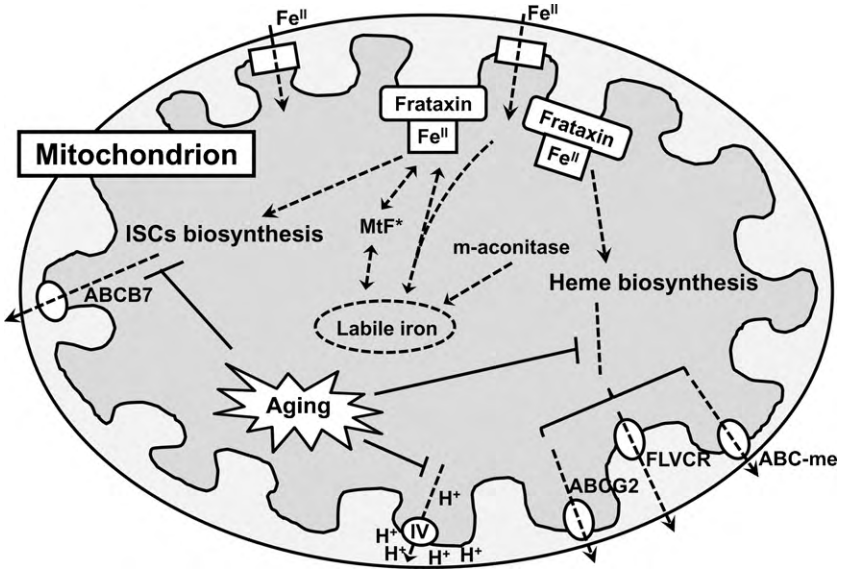
Table 1
Summary of studies reporting an association of iron accumulation, mitochondrial dysfunction and aging.

Stress	Pathway/mechanism	Effects	Prevention	Models	Selected references
Frataxin deficiency	Mitochondrial ISCs defects, decreased Mn-SOD activity	Increased iron levels, increased protein carbonylation	Copper and manganese treatments	Yeast	Napoli et al. (2006), Irazusta et al. (2009)
Paraquat	Iron release from m-aconitase	Increased mitochondrial iron, cell death	Iron chelation	Cell line	Cantu et al. (2009)
Aging	Mitochondrial ISCs defects trigger the activation of the iron regulon	Increased iron uptake, genomic instability	N/A	Yeast	Veatch et al. (2009)
Aging	N/A	Increased mitochondrial iron, permeability transition	CR	Rat	Seo et al. (2008), Xu et al. (2008)
Aging	Inactivation or degradation of IRPs	Free iron overload, increased ferritin, decreased transferritin, decreased lysosomal activity	N/A	Rat and mouse	Chen et al. (2009)
Aging	Deficiency in mitochondrial heme synthesis	Increased iron levels, increased ferrochelatase, loss of complex IV	N/A	Cell line and rat	Bitar and Weiner (1983), Atamna et al. (2001, 2002a)
Aging	N/A	Increased labile iron	N/A	Human	Doulias et al. (2008)

Abbreviations: m-aconitase, mitochondrial-aconitase; IRPs, iron-regulatory proteins; SOD, superoxide dismutase; CR, calorie restriction; N/A, not available; ISCs, iron–sulfur clusters.

to proteins or escaped from storage sites becomes redox-active, and may be harmful, particularly in the presence of high concentration of hydrogen peroxide within the same compartment (Sohal et al., 1999; Kakhlon and Cabantchik, 2002; Doulias et al., 2008). Several studies reported iron accumulation with age in mitochondria in rat substantia nigra (Schipper et al., 1998) and skeletal muscle (Seo et al., 2008) as well as human subcortical brain tissue (Schipper and Cisse, 1995). Given the fact that labile iron has a strong catalytic potential to generate ROS, iron overload may result in catastrophic cellular damage via increased oxidative stress accrual.

Since labile iron is transient and exists in dynamic equilibrium with various cellular components, early attempts to identify the labile iron pool were based on cell-disruptive methods, which in turn alter the equilibrium between free and bound iron, as well as the Fe^{II}/Fe^{III} redox state (Rothman et al., 1992; Kozlov et al., 1992; Sohal et al., 1999). Nondisruptive techniques that rely on the application of fluorescent metalosensors have been developed to estimate the intracellular chelatable iron (Epsztejn et al., 1997; Kakhlon and Cabantchik, 2002). Changes in labile iron in cells and tissues can be visualized by fluorescent probes, including phen green SK and calcein (Petrat et al., 2001, 2002a) since the ferrous iron quenches the fluorescence. However, these fluorophores also bind to other divalent cations like Cu, Ni and Co, which raises an issue of their selectivity (Breuer et al., 1995). The development of iron-sensitive fluorescent probes specifically targeting mitochondria has allowed significant advances in the study of labile iron (Petrat et al., 2002b; Rauen et al., 2007). Probes are comprised of a fluorescent group coupled with a high-affinity iron chelator and must fulfill several requirements. Firstly, probes must be lipophilic and highly membrane-permeable (Petrat et al., 2001). Secondly, fluorescent groups must possess a net positive charge and be electophoretically driven into mitochondria due to the inside negative membrane potential (Dykens and Stout, 2001). Thirdly, chelators must possess relatively high affinity for iron and be able to compete with endogenous ligands (i.e., pyruvate, phosphate,



Scheme 1. Schematic illustration of mitochondrial iron dyshomeostasis with aging. Iron is transported into the mitochondrial matrix by iron importers (e.g. mitoferrin) where it can be directed to different pathways, including storage in frataxin, iron–sulfur cluster (ISC) biosynthesis, heme metabolism, mitochondrial ferritin (MtF) or other currently unknown pathways. The ISCs can be exported to the cytoplasm by ABCB7. Heme is thought to be exported from the mitochondrion by several pathways, including ABCG2, the feline leukemia virus subgroup C receptor (FLVCR) and ABC-me. Defects in these transporters or defective biosynthesis of heme and ISCs with age impair mitochondrial iron homeostasis and lead to cellular degeneration. Increased labile iron with age, especially in mitochondria, has a strong potential to catalyze the generation of reactive oxygen species (ROS), resulting in cellular damage.