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Review article

Mitochondrial ferritin in neurodegenerative diseases☆

Hongkuan Yang[a,b], Mingchun Yang[a,b], Hongpeng Guan[a,b], Ziyi Liu[a,b], Shiguang Zhao[b], Shigeko Takeuchi[a], Daijiro Yanagisawa[a], Ikuo Tooyama[a,*]

[a] Molecular Neuroscience Research Center, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu 520-2192, Japan
[b] Department of Neurosurgery, 1st Affiliated Hospital, Harbin Medical University, Harbin 150001, China

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ABSTRACT

Mitochondrial ferritin (FtMt) is a novel protein encoded by an intronless gene mapped to chromosome 5q23.1. Ferritin is ubiquitously expressed; however, FtMt expression is restricted to specific tissues such as the testis and the brain. The distribution pattern of FtMt suggests a functional role for this protein in the brain; however, data concerning the roles of FtMt in neurodegenerative diseases remain scarce. In the human cerebral cortex, FtMt expression was increased in Alzheimer's disease patients compared to control cases. Cultured neuroblastoma cells showed low-level expression of FtMt, which was increased by H_2O_2 treatment. FtMt overexpression showed a neuroprotective effect against H_2O_2-induced oxidative stress and Aβ-induced neurotoxicity in neuroblastoma cells. FtMt expression was also detected in dopaminergic neurons in the substantia nigra and was increased in patients with restless legs syndrome, while FtMt had a protective effect against cell death in a neuroblastoma cell line model of Parkinson's disease. FtMt is involved in other neurodegenerative diseases such as age-related macular degeneration (AMD), with an FtMt gene mutation identified in AMD patients, and Friedreich's ataxia, which is caused by a deficiency in frataxin. FtMt overexpression in frataxin-deficient cells increased cell resistance to H_2O_2 damage. These results implicate a neuroprotective role of FtMt in neurodegenerative diseases.

Contents

1. Introduction

Iron is the most abundant transition metal in the brain, and its concentration increases with aging (Connor et al., 1990; Zecca et al., 2004) as well as in neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Batista-Nascimento et al., 2012; Kell, 2010; LeVine, 1997; Sian-Hulsmann et al., 2011; Zecca et al., 2004). Free iron is a source of oxidative stress and subsequent cell damage; therefore, under physiological conditions, iron is normally bound to proteins such as ferritin and transferrin (Connor et al., 1990, 1992). Indeed, the presence of excessive free iron is a hallmark of aging diseases because it is not correctly stored in ferritin cores such as the ferric iron oxide redox-inert form (Altamura and Muckenthaler, 2009; Casadesus et al., 2004; Huang et al., 2004; Smith et al., 1997). Although excess iron is stored primarily in the cytoplasm, most of the metabolically active iron in cells is processed in the mitochondria.

Mitochondrial ferritin (FtMt) is a novel protein encoded by an intronless gene mapped to chromosome 5q23.1 (Levi et al., 2001).

* Corresponding author. Tel.: +81 077 548 2330; fax: +81 077 548 2331.
E-mail address: kinchan@belle.shiga-med.ac.jp (I. Tooyama).

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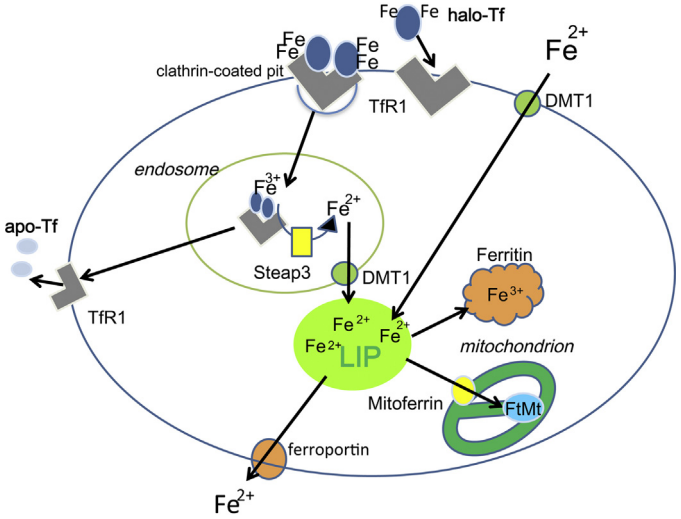

Fig. 1. Iron metabolism in neurons. Transferrin binds Fe(III) to form transferrin/transferrin receptor complexes, which are endocytosed into cell via the invagination of clathrin-coated pits. In the acidic endosome, Fe(III) is reduced to Fe(II) by Steap 3 and transported by DMT1 to labile iron pool (LIP) in the cytoplasm, where Fe(II) is stored in ferritin or imported into mitochondria by mitoferrin. Non-transferrin-bound Fe(II) at the cell surface is imported directly into the LIP by DMT1 on the cell surface.

The FtMt 242-amino acid precursor protein has a predicted molecular weight of 30 kDa and 79% homology to H-chain ferritin. This precursor protein has a positively charged leader sequence of 60 amino acids and is imported into the mitochondria where it is proteolytically cleaved to a ~22-kDa mature protein. The cleaved FtMt forms H-type ferritin shells with ferroxidase activity that most likely sequesters potentially harmful free iron (Corsi et al., 2002; Drysdale et al., 2002; Levi and Arosio, 2004).

Ferritin composed of H-type and L-type subunits is widely distributed in the body. However, FtMt gene expression is low in iron-storage organs such as the liver and spleen but can be detected in specific tissues such as the testis, kidney, heart, thymus, and brain (Campanella et al., 2004; Drysdale et al., 2002; Hahn et al., 2004). This distribution pattern suggests that FtMt plays a functional role in these tissues, including the brain; however, little information is currently available regarding the roles of FtMt in neurodegenerative diseases.

This paper aims to review recent research regarding FtMt functions in neurodegenerative diseases such as AD. An understanding of the various roles of FtMt may provide new insight into pathogenic mechanisms and therapeutic strategies for AD and other neurodegenerative diseases.

2. Iron metabolism in the brain

First, we summarize iron metabolism in the brain. Fig. 1 illustrates the mechanisms of iron metabolism and iron regulatory proteins in neurons, and Table 1 summarizes the distributions, subcellular localizations and iron regulation functions of iron-related proteins.

Iron in serum is bound to iron transport proteins such as transferrin and lactotransferrin. Transferrin binds two atoms of Fe(III) (halo-transferrin), and two halo-transferrin molecules bind to one transferrin receptor molecule on the plasma membrane of cells. The halo-transferrin/transferrin receptor complex becomes incorporated into a clathrin-coated pit, which invaginates and is then endocytosed to fuse with an endosome (Fig. 1). Another pathway of iron uptake is through the divalent metal iron transporter 1 (DMT1), which only binds ferrous iron Fe(II). Therefore, Fe(III) has to be reduced prior to cell entry via DMT1 (Garrick, 2011).

In the brain, iron must be transported from the serum through the blood brain barrier (BBB). Endothelial cells in the brain capillary and choroid plexus cells express transferrin receptors (Giometto et al., 1990; Moos, 1996; Moos et al., 1998; Rothenberger et al., 1996), while lactoferrin receptors are present in brain capillaries, neurons, and several glial cells (Faucheux et al., 1995). Lactotransferrin may also play a role in iron transport at the BBB (Fillebeen et al., 1999), and brain capillaries express the low-density lipoprotein-related protein (LRP), which is a receptor for lactotransferrin (Tooyama et al., 1993, 1995) and other ligands such as α2-macroglobulin, apolipoprotein E (ApoE), amyloid precursor protein (APP), plasminogen activators, plasminogen activator inhibitor I (PAI-1), lipoprotein lipase, receptor-associated protein (RAP), interleukin-1β, transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) (Rebeck et al., 1993). These ligands are taken up by cells via receptor-mediated endocytosis.

The sites of DMT1 expression remain controversial. Burdo et al. (2001) demonstrated the presence of DMT1 in brain capillaries (Burdo et al., 2001); however, Moos and his colleagues reported that brain capillary endothelial cells do not express DMT1 (Moos and Morgan, 2004; Moos et al., 2006). The latter authors also suggested that iron passes through the BBB without the involvement of DMT1 (Moos et al., 2006), and they noted the importance of interactions between endothelial cells and astrocytes in the BBB transit of iron (Moos et al., 2007). Low molecular-weight molecules such as ATP and citrates help to mediate the release of iron from transferrin into the brain extracellular fluid (Crichton et al., 2011; Moos and Morgan, 1998).

As shown in Table 1, ferritin (Connor et al., 1990, 1992; Han et al., 2002) and transferrin (Dwork et al., 1988; Connor et al., 1990, 1992) have been shown to be present in neurons and glia. Neurons also express transferrin receptors and take up transferrin-bound iron into the endosome by receptor-mediated endocytosis (Dwork et al., 1988). In the acidic endosome, Fe(III) is released from proteins and reduced to Fe(II) by Steap 3, a member of the Steap family of metalloreductases (Ohgami et al., 2006). Fe(II) in the cytoplasm transiently enters the labile iron pool (LIP) where iron is bound to low-molecular-mass intracellular chelates such as citrate, various peptides, ATP, AMP, and pyrophosphate. Neurons also express DMT1 and absorb iron in the cytoplasm, with excess ferrous iron exported from the cytoplasm by ferroportin in the cell membrane (Moos et al., 2007).

Cells primarily use the iron located in mitochondria for the synthesis of heme and iron–sulfur clusters, and the entry of iron into mitochondria requires the solute carrier (SLC) transporter, mitoferrin (Richardson et al., 2010). As a ubiquitous protein, the ATP-binding cassette transporter ABCB7 may also be involved in iron export from the mitochondria to the cytosol, and a deficiency in this transporter potentially causes mitochondrial iron accumulation (Cavadini et al., 2007). Cells also store and detoxify excess intracellular iron in the cytoplasm within ferritin composed of H- and L-subunits. H-ferritin possesses ferroxidase activity, and L-ferritin provides a nucleation center (Fig. 1).

Mitochondria contain another type of ferritin, FtMt, which also possesses ferroxidase activity. FtMt overexpressed in HeLa cells was translocated into mitochondria and incorporated with iron (Corsi et al., 2002), and simultaneously, cytosolic ferritin levels decreased and transferrin receptor levels increased (Corsi et al., 2002). Nie et al. (2005) also reported that a stable cell line overexpressing mouse FtMt had increased mitochondrial iron and decreased cytosolic iron together with increased transferrin receptor levels and decreased cytosolic ferritin (Nie et al., 2005). These results suggest that FtMt together with cytosolic ferritin and the