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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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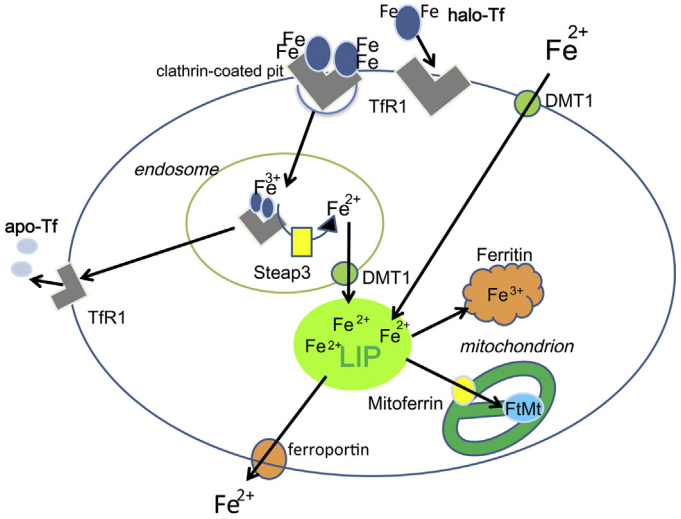

Fig. 1. Iron metabolism in neurons. Transferrin binds Fe(III) to form transferrin/transferrin receptor complexes, which are endocytosed into cell via the invagination of clathrin-coated pits. In the acidic endosome, Fe(III) is reduced to Fe(II) by Steap 3 and transported by DMT1 to labile iron pool (LIP) 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

Table 1
Distribution, subcellular localization, and iron-regulatory functions of some iron-related proteins in the brain.

	Distribution in brain	Subcellular localization	Iron regulation	References
Ferritin	Neuron, Glia	Cytoplasm	Iron storage; Ferroxidase activity	Connor et al. (1990, 1992) and Han et al. (2002)
FtMt	Neuron, Glia	Mitochondria	Iron storage; Ferroxidase activity	Drysdale et al. (2002), Santambrogio et al. (2007) and Wang et al. (2011)
Transferrin	Neuron, Glia, Choroid plexus	Cytoplasm	Iron binding and transport	Dwork et al. (1988) and Connor et al. (1990, 1992)
Transferrin R	Neuron, Capillary, Choroid plexus	Membrane	Receptor-mediated endocytosis and exocytosis	Giometto et al. (1990), Moos (1996), Moos et al. (1998) and Rothenberger et al. (1996)
Lactoferrin	Neuron, Microglia	Cytoplasm	Iron binding and transport	Kawamata et al. (1993), Leveugle et al. (1994) and An et al. (2009)
Lactoferrin R (and LRP)	Neuron, Glia, Capillary	Membrane	Receptor-mediated endocytosis	Faucheux et al. (1995) and Tooyama et al. (1993, 1995)
DMT1	Neuron, Capillary?	Membrane	Internalization of iron	Burdo et al. (2001)
Ferroportin	Neuron	Membrane	Iron exporting carrier	Moos et al. (2007)
Mitoferrin	Neuron?	Mitochondria	Transport of iron into mitochondria	Richardson et al. (2010)

FtMt, mitochondrial ferritin; R, receptor; LRP, low-density lipoprotein-related protein; DMT1, divalent metal iron transporter.

transferrin receptor cooperatively regulate iron homeostasis in both the cytoplasm and in mitochondria.

In the mouse brain, FtMt is expressed primarily in neurons (Santambrogio et al., 2007; Snyder et al., 2010) and to a lesser extent in glial cells (Snyder et al., 2010). The neuronal expression of FtMt is supported by other studies using human brain tissues (Snyder et al., 2009; Wang et al., 2011). As described above, FtMt has restricted tissue expression compared with cytosolic ferritin, which is ubiquitously expressed. Additionally, unlike cytosolic ferritin, FtMt is not regulated by iron-dependent translational control because the FtMt gene lacks the classical stem-loop iron-regulatory element (Drysdale et al., 2002). The unique distribution pattern of mitochondrial ferritin suggests that FtMt expression may be regulated at the transcriptional level by tissue- and cell type-specific transcription factors.

Excessive iron in specific brain cellular constituents, including mitochondria, leads to the generation of toxic free radicals, resulting in cell damage that eventually causes neurodegenerative diseases (Ames et al., 1993; Crichton et al., 2011; Crichton and Ward, 2006; Honda et al., 2004; Huang et al., 2004). Specifically, Fe(II) reacts with hydrogen peroxide (H_2O_2) via the Fenton reaction to generate reactive and harmful hydroxyl radicals ($OH^{\bullet}$) (Goldstein et al., 1993; Winterbourn, 1995; Winterbourn et al., 2002); however, superoxide (O_2^-) reacts with Fe(III) in the Haber–Weiss reaction to regenerate Fe(II) (Kehrer, 2000), causing a redox cycling of the iron.

3. Mitochondrial ferritin in AD

Iron accumulation and oxidative stress in the brains of AD sufferers have been correlated with AD progression (Altamura and Muckenthaler, 2009; Bartzokis et al., 2000; Casadesus et al., 2004; Crichton et al., 2011; Deibel et al., 1996; Honda et al., 2004, 2005; Huang et al., 2004; Kell, 2010; LeVine, 1997). In addition, abnormalities in iron-regulating proteins, including transferrin (Connor et al., 1992), melanotransferrin (Jefferies et al., 1996; Yamada et al., 1999), lactotransferrin (An et al., 2009; Kawamata et al., 1993), iron regulatory proteins (IRPs) (Pinero et al., 2000; Smith et al., 1998), and ferritin (Connor et al., 1992) occur in the brain of AD sufferers.

Experimental evidence suggests an interaction between iron and amyloid beta-protein (Aβ) metabolism in the brain. Iron accumulation occurs in the same regions of the brain characterized by Aβ deposition (Huang et al., 2004; LeVine, 1997), and Aβ binds iron directly in vitro (Exley, 2006; Jiang et al., 2009). The level of intracellular APP is also tightly regulated by iron via the binding of iron directly to the APP 5′-UTR, which governs the rate of APP translation. The expression of APP is upregulated by increased iron; however, it is repressed by iron chelation (Rogers et al., 2002). Furin is an enzyme belonging to the subtilisin-like proprotein convertase family and has been linked to iron homeostasis and Aβ production (Crichton et al., 2011). Low and high cellular iron levels increase and decrease the activity of furin, respectively. In turn, furin enhances α-secretase to stimulate the non-amyloidogenic pathway. Therefore, high cellular iron induces the reduction of furin activity and subsequent Aβ production (Silvestri and Camaschella, 2008; Silvestri et al., 2008). In the brains of AD patients and Tg2576 mice, furin mRNA levels were significantly lower compared to the levels in the controls (Hwang et al., 2006), which is consistent with the different iron accumulation patterns in AD patients and controls. Aβ is a potent generator of reactive oxygen species (Hensley et al., 1994) and reactive nitrogen species (Combs et al., 2001), and in turn, oxidative stress promotes intracellular accumulation and production of Aβ (Misonou et al., 2000; Silvestri and Camaschella, 2008).

Overall, excess iron may induce an autotoxic loop that results in neurodegeneration (Fig. 2), and the mitochondrion is one of the main organelles where such an autotoxic loop may occur because of the role mitochondria play in iron utilization.

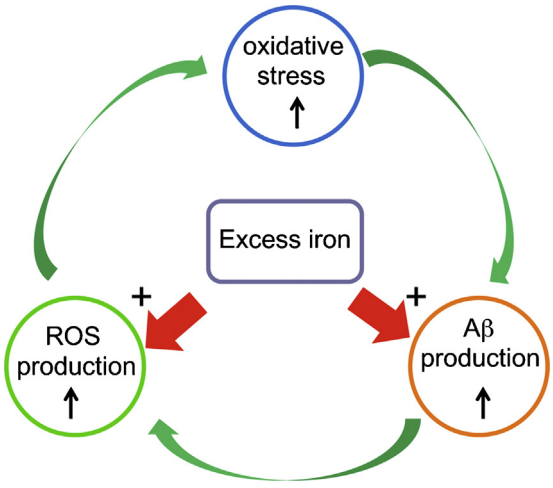

Fig. 2. An autotoxic loop may occur in the brain of AD sufferers. Ferrous iron generates oxidative stress by producing reactive oxygen species (ROS) via Fenton and Haber–Weiss reactions. High cellular iron upregulates the expression of amyloid precursor protein, which activates the amyloidogenic pathway, leading to increased Aβ production (Silvestri and Camaschella, 2008; Silvestri et al., 2008). Aβ is neurotoxic to the brain via the induction of ROS production (Hensley et al., 1994), and oxidative stress promotes further intracellular accumulation and production of Aβ (Misonou et al., 2000; Silvestri and Camaschella, 2008).

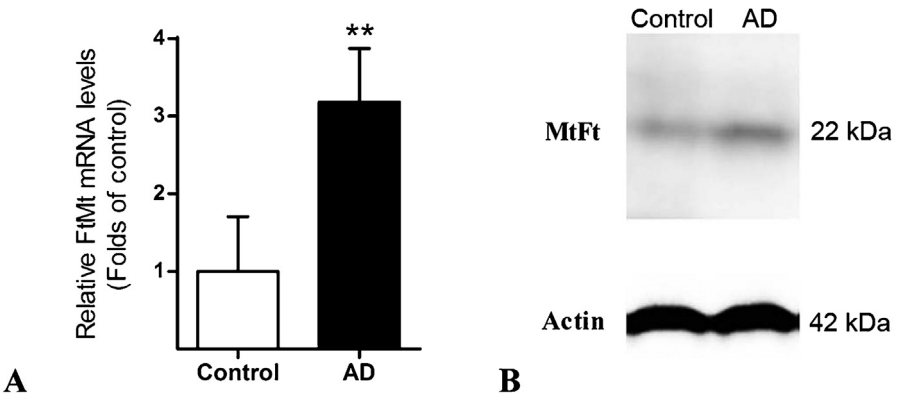

Fig. 3. Expression levels of FtMt mRNA (A) and protein (B) in the cerebral cortex of AD patients and control cases. (A) Expression in the temporal cortex of AD patients ($n = 5$) is significantly higher compared to control cases ($n = 5$). To correct for mRNA variability, the amount of FtMt mRNA obtained from each sample was divided by the amount of β-actin mRNA. The relative value was calculated with the following formula: (FtMt mRNA)/(β-actin mRNA) × 10^5. An asterisk indicates significant difference from the control ($^*P < 0.05$; $^{**}P < 0.01$). (B) The expression level of FtMt protein in the temporal cortex of AD patients is higher compared to the level in the control cases. Proteins (50 μg per lane) from the temporal cortex of an AD and a control case were electrophoresed on 15% SDS-polyacrylamide gels and were then transferred to a polyvinylidene difluoride membrane (Immobilon-P, Nippon Millipore Ltd., Tokyo, Japan). We used the anti-FtMt rabbit polyclonal antibody at 1:1000 (A93251Hu, Uscn, Wuhan, China) and ECL Western blotting detection reagents (SuperSignal West Pico, Thermo Scientific, Rockford, IL, USA).

FtMt plays a profound role in regulating iron homeostasis and oxidative stress; therefore, it may participate in both the pathogenesis and the pathological progression of AD. However, limited data are available regarding the relationship between FtMt and AD. We recently demonstrated by in situ hybridization that the FtMt gene was primarily expressed in neurons located in the temporal cortex in both AD patients and normal individuals (Wang et al., 2011), although this expression was greater in the AD sufferers (Fig. 3). These observations support the possible involvement of FtMt in AD pathogenesis.

Increased expression of FtMt was induced by H_2O_2 in the human neuroblastoma IMR-32 cell line (Fig. 4). Interestingly, this induction occurred when H_2O_2 was used in combination with $A\beta_{1-42}$ but not with $A\beta_{1-42}$ alone (Wang et al., 2011). The treatment of neuroblastoma cells with H_2O_2 in combination with Aβ is likely to induce intense oxidative stress. Indeed, the increased level of oxidative stress observed in the brains of AD sufferers may reflect a similar induction of FtMt expression in the cortex. The result is also consistent with animal experiments suggesting that Aβ alone is insufficient to induce AD-like symptoms due to the antioxidant defense activity present in the brain. Aβ-independent oxidative stress reduces the effectiveness of this antioxidant defense system, which allows the Aβ peptide to induce AD-like symptoms (Lecanu et al., 2006).

FtMt expression is normally low in neuroblastoma cell lines but is stimulated by oxidative stress (Wang et al., 2011). The overexpression of FtMt in IMR-32 cells protected these cells from neuronal death induced by H_2O_2 (Fig. 5) and $A\beta_{25-35}$ (Wu et al., 2013). In turn, knockdown of FtMt significantly enhanced $A\beta_{25-35}$-induced neurotoxicity by dysregulation of iron homeostasis, enhanced oxidative stress, and increased cell apoptosis (Wu et al., 2013). These data indicate that FtMt is induced under pathological conditions associated with mitochondrial iron loading or oxidative stress and may play a neuroprotective role against oxidative stress and Aβ neurotoxicity. Although increased endogenous FtMt expression occurs upon incubation with H_2O_2, we were not able to rescue cell viability unless FtMt was expressed prior to H_2O_2 treatment (Wang et al., 2011). One explanation for this observation is that exogenous H_2O_2-induced cell death occurs before FtMt exerts its neuroprotective effect. Therefore, it appears that the overexpression of FtMt prior to cell treatment with H_2O_2 has a greater protective effect than endogenous FtMt expression.

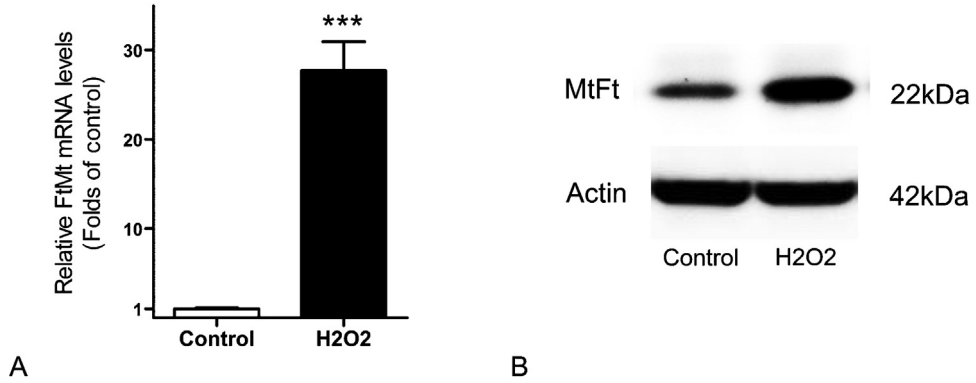

Fig. 4. FtMt mRNA (A) and protein (B) expression levels in cultured cells. Compared to the untreated control, the FtMt mRNA ($^{***}P < 0.001$) and protein expression levels are significantly induced after H_2O_2 treatment. IMR-32 cells were seeded in 60-mm dishes at a density of 500,000 and grown for 48 h. Next, 200 μM H_2O_2 was added, and the cells were incubated for 30 min. Medium was replaced with fresh medium. Total protein and RNA was extracted from 6 independent dishes after an 18-h recovery period. RNA solution was treated with DNase to eliminate contaminating DNA. The FtMt mRNA (A) and protein (B) expression levels were detected by real-time PCR using TaqMan probes and Western blotting, respectively.

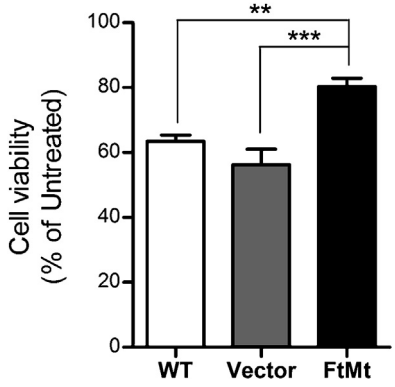

Fig. 5. The effect of FtMt expression on cell viability after H_2O_2 treatment. The overexpression of FtMt in IMR-32 cells increased cell viability compared to wild-type cells (**$P < 0.01$) and empty vector-transfected cells (***$P < 0.001$). IMR-32 cells were seeded in 96-well plates at a density of 10,000 cells and grown for 24 h, and then the cells were transiently transfected with either an FtMt expression plasmid or an empty vector. At 24 h post-transfection, cells were treated with or without 300 μM H_2O_2 for 30 min, and then the cells were recovered for 18 h in fresh medium. Cell viability was measured using the MTT assay. The data are expressed as the percentage of untreated cells ($n = 8$) ± standard deviation in each group.

4. Mitochondrial ferritin in PD and restless legs syndrome (RLS)

PD has many features in common with syndromes associated with the disruption of iron homeostasis, mitochondria dysfunctions, and oxidative stress (Lin and Beal, 2006; Sian-Hulsmann et al., 2011; Zhang et al., 2000). Iron concentrations in the substantia nigra and globus pallidus are higher than the levels in other brain regions. PD brains show increased levels of iron (Gotz et al., 2004; Dexter et al., 1987), which was found to accumulate within Lewy bodies, which are the characteristic hallmarks of PD (Castellani et al., 2000). Studies have also shown that iron promotes the aggregation of α-synuclein, which is the primary component of Lewy bodies, while the aggregation of α-synuclein is blocked by iron chelation (Ostrerova-Golts et al., 2000; Sangchot et al., 2002).

The neuroblastoma SH-SY5Y cell line model of PD is induced by 6-hydroxydopamine (6-OHDA), a neurotoxin that causes selective death in catecholamine-containing neurons. The overexpression of FtMt significantly prevented the alteration of iron redistribution and caused cytosolic iron deficiency in the SH-SY5Y cell line model of PD (Shi et al., 2010). FtMt also strongly decreased production of reactive oxygen species and lipid peroxidation as well as repressed the loss of mitochondrial membrane potential. Moreover, FtMt expression regulates apoptotic signaling by increasing the level of anti-apoptotic protein, Bcl-2, which prevents caspase-3 activation, eventually rescuing the neuronal cells (Shi et al., 2010).

RLS is associated with the urge to move legs accompanied by abnormal sensations in the legs, particularly at rest. Transcranial ultrasounds (Schmidauer et al., 2005) and magnetic resonance imaging (MRI) (Allen et al., 2001) demonstrated decreased iron levels in the substantia nigra of patients with RLS; however, a neuropathological study of postmortem human brains revealed increased FtMt and decreased H-ferritin in the substantia nigra of these patients (Snyder et al., 2009). The overexpression of FtMt decreases cytosolic iron levels (Corsi et al., 2002; Nie et al., 2005); therefore, Snyder et al. (2009) suggested that FtMt may contribute to the reduced cytosolic iron levels in the substantia nigra neurons of patients with RLS (Snyder et al., 2009).

Thus far, FtMt studies suggest that the increased expression of this protein in AD, PD, and other neurological disorders likely plays a neuroprotective role against the toxicity of iron overload and oxidative stress via iron sequestration. In contrast, in RLS, increased FtMt expression may be linked to disease occurrence rather than neuroprotection. Nevertheless, these interesting findings implicate FtMt in the pathogenesis of neurological diseases. In addition, studies into the mechanism by which FtMt expression is regulated should be prioritized because, unlike other ferritins, FtMt lacks iron-responsive elements in its mRNA and is not regulated directly by iron.

5. Mitochondrial ferritin in other diseases

Iron accumulation with age contributes to the pathogenesis of age-related macular degeneration (AMD) by inducing considerable oxidative stress (He et al., 2007). Postmortem studies showed an increased total iron level in AMD-affected maculas compared to healthy maculas, and a portion of this iron was chelatable; therefore, iron chelation may be a potential therapy for AMD (Hahn et al., 2003). Immunohistochemistry demonstrated that FtMt localizes to the inner segments of the retinas and showed increased FtMt with iron accumulation (Hahn et al., 2004). An FtMt gene mutation was also identified in patients affected by AMD, suggesting that dysfunctional FtMt may be associated with AMD pathogenesis via reduced protection from iron-dependent oxidative stress in mitochondria (Stenirri et al., 2012).

High-level FtMt expression is also associated with the iron-loaded erythroblasts in patients with sideroblastic anemia but is not observed in normal erythroblasts (Cazzola et al., 2003). Sideroblastic anemia is a disorder characterized by mitochondrial iron overload and high levels of FtMt expression exclusively in ringed sideroblasts. FtMt has been proposed to protect the mitochondria from damage caused by iron loading in this disease (Cazzola and Invernizzi, 2011; Cazzola et al., 2003; Napier et al., 2005).

Friedreich's ataxia (FRDA) is a disorder characterized by mitochondrial iron overload caused by a deficiency of frataxin, which is a mitochondrial protein involved in iron handling. Human FtMt expression in frataxin-deficient yeast cells prevented the development of mitochondrial iron overload, preserved mitochondrial DNA integrity, and increased cell resistance to H_2O_2 (Campanella et al., 2004). Similarly, the effects of silencing frataxin expression in HeLa cells were rescued by inducing the expression of human FtMt, which indicates a protective role of FtMt in mitochondrial iron-loaded cells (Campanella et al., 2009; Zanella et al., 2008).

6. Conclusions

FtMt is a novel protein localized in mitochondria. FtMt is expressed in restricted tissues including the brain. FtMt lacks iron regulatory elements, and its expression is increased by oxidative stress. The unique distribution and stress-inducing property of its expression suggest that FtMt may play an important physiological and pathological role in the brain. Iron and oxidative stresses are strongly correlated with numerous neurological diseases, not only those mentioned in this review, indicating that FtMt may be involved in the pathogenesis of a range of diseases. However, information concerning the role of FtMt in neurological pathology is still limited. FtMt is increased in the cerebral cortex of AD patients and in the substantia nigra of individuals with PD and RLS. The presence of FtMt prevents cell death induced by oxidative stress and neurotoxic proteins, although under some circumstances, FtMt is linked to the occurrence of selected disorders such as RLS. Improved understanding of the role of FtMt may therefore provide new insights into the pathogenesis and therapeutic strategies for AD and other neurodegenerative diseases.

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