J Bioenerg Biomembr (2011) 43:593–599
DOI 10.1007/s10863-011-9394-z

MINI REVIEW

SOD1 and mitochondria in ALS: a dangerous liaison

Maria Teresa Carrì · Mauro Cozzolino

Published online: 12 November 2011

Abstract Mutant Cu,Zn superoxide dismutase (mutSOD1) is found in a subset of patients with familial amyotrophic lateral sclerosis (ALS), a fatal progressive paralysis due to loss of motor neurons. In the present article, we review existing evidence linking the expression of mutSOD1 to the many facets of mitochondrial dysfunction in ALS, with a focus on recent studies suggesting that the association and misfolding of the mutant protein (and possibly of the wild type protein as well) within these organelles is causally linked to their functional and structural alterations. Energy deficit, calcium mishandling and oxidative stress are paralleled by alteration in mitochondrial motility, dynamics and turnover and most probably lead to mitochondria-dependent cell death. Thus, the development of new, selective mitochondria-targeted therapies may constitute a promising approach in the treatment of SOD1-linked ALS.

Keywords Amyotrophic lateral sclerosis · Mitochondria · SOD1 · Motor neuron

SOD1 and ALS

Mutations in the gene coding for the ubiquitously expressed, antioxidant enzyme SOD1 (Cu,Zn superoxide dismutase, EC1.15.1.1) are the most frequent cause of familial Amyotrophic lateral sclerosis (ALS), one of the most common adult-onset motor neuron diseases, characterized by spasticity, generalized muscle atrophy and progressive paralysis due to degeneration of specific motoneuronal populations in the cortex and spinal cord.

Mutations in the SOD1 gene were the first discovered genetic cause for ALS (Rosen et al. 1993) and thus cell and animal models based on the expression of one out of the more than 130 different mutant SOD1 (mutSOD1) reported up to date (http://alsod.iop.kcl.ac.uk/) have been developed and widely studied. Translation of therapy from rodents expressing mutSOD1 to patients has been quite disappointing (Bendotti and Carri 2004; Carri et al. 2006) and thus studies on SOD1-based models are now being paralleled by studies in models built on the expression of other ALS-associated mutations, such as TDP43 and FUS (Sreedharan et al. 2008; Vance et al. 2009; Zhou et al. 2010a). Nonetheless, the mutSOD1 models are still a valuable tool for basic research, and have served for instance to the demonstration that ALS cannot be considered a pure a motor neuron disease because alteration of non-neuronal cells also contributes to the progression of symptoms and final outcome (Ilieva et al. 2009). Thus, it is possible that the noxious effect of mutant SOD1 is different in different cell populations and this would explain why so many, although interconnected, pathogenic mechanisms have been proposed to explain the ALS clinical phenotype. Indeed, diverse pathways such as oxidative stress, protein misfolding and aggregation, glutamate-mediated excitotoxicity, alterations of the endoplasmic reticulum and cytoskeleton, aberrant axonal transport, altered RNA metabolism, dysfunction of the ubiquitin proteasome pathway, neuromuscular junction abnormalities, immune system deficiency and neuroinflammation are thought to play a role in ALS (Cozzolino et al. 2008b;

M. T. Carrì · M. Cozzolino (✉)
Fondazione Santa Lucia IRCCS,
c/o CERC, Via del Fosso di Fiorano 64,
00143 Rome, Italy
e-mail: m.cozzolino@hsantalucia.it

M. T. Carrì
Department of Biology, University of Rome "Tor Vergata",
Via della ricerca scientifica,
00133 Rome, Italy

Kiernan et al. 2011). Interestingly, mitochondrial dysfunction may have a role in many, if not all of the above mechanisms (Shi et al. 2010b).

Mitochondrial dysfunction in mutSOD1-ALS

For almost 40 years after its first description by Irwin Fridovich (McCord and Fridovich 1969), the function of wild type SOD1 has been studied in relation to its predominant cytosolic localization. However, a small fraction of this abundant, ubiquitous enzyme resides in mitochondria as clearly demonstrated in a pioneering paper by Fridovich himself (Okado-Matsumoto and Fridovich 2001; Weisiger and Fridovich 1973) and by many others in recent years (Higgins et al. 2002; Jaarsma et al. 2001; Mattiazzi et al. 2002; Okado-Matsumoto and Fridovich 2001). Many mutSOD1s are also localized in various mitochondrial subcompartments in a similar or even larger extent than the wild type enzyme (Bergemalm et al. 2006; Deng et al. 2006; Ferri et al. 2006; Higgins et al. 2002; Israelson et al. 2010; Jaarsma et al. 2001; Liu et al. 2004; Pasinelli et al. 2004; Vande Velde et al. 2008; Vijayvergiya et al. 2005). Thus, because of the multiple tasks performed by mitochondria in energy metabolism, calcium homeostasis and regulation of the intrinsic apoptotic pathway and because mutation causes an increase in the amount of SOD1 associated with mitochondria, it is possible that the mitochondria-SOD1 liaison is at the centre of ALS pathogenesis.

Indeed, there is now compelling evidence that mitochondrial perturbations participate in the mechanisms of degeneration in ALS patients and in cell and animal models for mutSOD1-linked ALS. ALS mitochondria appear degenerated, with an altered ultrastructure (reviewed in (Magrane and Manfredi 2009), and may become integrated into Bunina bodies, that are the only ALS-specific histopathology hallmark and may represent mitophagic inclusions (Okamoto et al. 1990). Interestingly, overexpression of mutSOD1 induces the activation autophagy, as measured by the activation of LC3 (microtubule-associated protein1 light chain 3) and the association with mitochondria of PTEN-induced kinase (PINK1) (Ferri et al. 2010; Morimoto et al. 2010; Morimoto et al. 2007; Pizzasegola et al. 2009) a protein that may modulate the process of removal of mis-functional mitochondria through autophagy (mitophagy) (Deas et al. 2011). Mitophagy may be activated following the parallel disruption of morphology and functionality of mitochondria, where expression of mutant SOD1 elicits a clear deficit in the electron transport chain (ETC) (Cozzolino et al. 2008b), mishandling of mitochondrial calcium (Grosskreutz et al. 2010) and activation of the apoptotic pathway (Shi et al. 2010a) (see below).

Mitochondrial SOD1 is mostly in the intermembrane space, although a small portion has been detected also on the cytoplasmic face of the outer membrane and in the matrix. How wild type and mutant SOD1 gain access to mitochondria in the absence of a canonical mitochondria-targeting signal, and what is the physiological function of this fraction of the enzyme, that has been classically considered the major cytosolic antioxidant, are both questions that need to be answered to fully understand the role of mutant SOD1 in the pathogenesis of ALS.

How and why SOD1 localizes into mitochondria

To enter each of the four mitochondrial compartments, i.e. the outer and inner membrane (OM and IM), the intermembrane space (IMS) and the matrix, mitochondrial proteins encoded by the nuclear genome utilized two types of targeting signals: amino terminal pre-sequences that are cleaved from the protein while entering mitochondria, or internal targeting sequences, that remain part of the fully matured protein (reviewed in (Schmidt et al. 2010). In the absence of an obvious mitochondrial targeting sequence, the import mechanism of SOD1 (and of its copper chaperon CCS) in mitochondria has been largely unknown until very recently, when it became clear that SOD1 enters mitochondria through the Erv1/Mia40 oxidative folding mechanism of import (Fig. 1). Indeed, CCS is imported in mitochondria by the Mia40/Erv1 pathway in a process that involves the formation of mixed disulfides between CCS and Mia40,

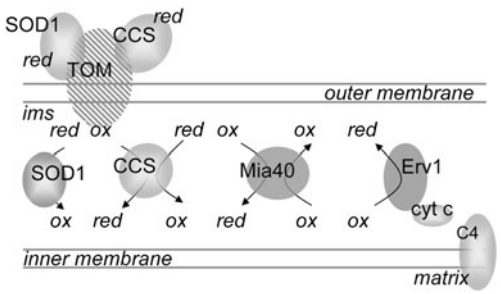

Fig. 1 The Erv1/Mia40 oxidative folding mechanism of protein import in mitochondria. The mitochondrial intermembrane space assembly (MIA) machinery is able to transfer electrons from reduced (*red*) and unfolded proteins, newly imported via the Translocase of the Outer Membrane (TOM), to the respiratory chain, finally leading to the oxidative folding and entrapment of the oxidized (*ox*) protein inside the intermembrane space (IMS). In this machinery, oxidized Mia40 acts as an oxidoreductase: it transfers disulphide bonds to the imported proteins and becomes reduced. Reduced Mia40 is then re-oxidized by the sulphydryl oxidase Erv1. The disulphide relay is coupled to the removal of electrons that are transferred from Erv1 to cytochrome c and then to the Cytochrome Oxidase complex IV (C4). CCS is among the substrates that are imported through the Erv1/Mia40 machinery. Oxidized CCS, in turn, transfers a disulfide bond to SOD1, which is thus oxidized, folded and trapped inside the IMS

and that is sensitive to oxygen concentrations (Kawamata and Manfredi 2008; Reddehase et al. 2009). In turn, the import of CCS leads the transport of SOD1 inside the IMS, as originally proposed by the group of Culotta (Field et al. 2003), by promoting the oxidative folding of the protein, a process involving cysteine residues of SOD1 and thus sensitive to redox conditions (Ferri et al. 2006; Kawamata and Manfredi 2008).

Human SOD1 has four cysteine residues: Cys57 and Cys146, that form an intramolecular disulfide bridge essential for the folding of the protein, and the two unpaired Cys6 and Cys111 residues, whose role has been mostly overlooked until very recently. Since cysteine residues are critical for the mitochondrial localization of small IMS proteins that are imported through the Mia40/Erv1 pathway, it is not surprising that SOD1 cysteines are connected to the process of SOD1 import. Indeed, all four cysteine residues seem to be important, since mutations in any of them bring as a consequence a decreased localization of SOD1 to mitochondria (Kawamata and Manfredi 2008).

The evolutionary reasons for the localization of wild type SOD1 in mitochondria are still partially obscure. As a consequence of physiological leakage of superoxide from the ETC, mitochondria are the major site of production of intracellular reactive oxygen species (ROS) and therefore need a robust antioxidant defense to prevent local oxidative stress that may impair protein function and membrane integrity and increase mitochondrial DNA damage. This defense has been traditionally considered as provided by the abundant, matrix-associated MnSOD (SOD2). This concept has been challenged in recent years by different observations in yeast and in mammals that support a role of SOD1 in the prevention of the oxidation of mitochondrial proteins and thus in the preservation of mitochondrial homeostasis (Aquilano et al. 2006; Kloppel et al. 2010; O'Brien et al. 2004). This role may be mostly relevant in neuronal cells, since mice lacking SOD1 (Sod1 −/−) show a distal motor neuropathy accompanied by decreased mitochondrial density and increased oxidative stress in mitochondria, that is rescued by SOD1 targeted to the mitochondrial intermembrane space (Fischer et al. 2011). These results are particularly interesting when considering mitochondrial damage caused by ALS-typical mutant SOD1.

Mutant SOD1 and mitochondria

As mentioned above, mutations in SOD1 associated with ALS seem to increase the ability of the protein to accumulate in mitochondria and to localize in different mitochondrial sub-compartments, and it is now widely accepted that an uncontrolled accumulation of mutSOD1s in mitochondria, or the accumulation inside mitochondria of a misfolded, aggregated form of SOD1 might represent a critical point in the pathogenesis of ALS.

Is this a consequence of an altered mechanism of mitochondrial import of SOD1 due to ALS-linked mutations, or is the trapping of mutSOD1s inside mitochondria caused by an inherent pro-aggregating property? Likely, both the mechanisms act concurrently, since it has been shown that the physiological regulation of mitochondrial localization of mutSOD1s by CCS is inefficient (Kawamata and Manfredi 2008), and that mutSOD1s associate with mitochondria in a partially unfolded, oligomeric state (Deng et al. 2006; Ferri et al. 2006; Furukawa et al. 2006). Interestigly, this fraction of the protein is sensitive to the pro-oxidant environment descending from mitochondrial alterations, such a shift in the ratio between reduced and oxidized glutathione (Ferri et al. 2006), which obviously has an important role in the overall mechanism of mitochondria protein import (Herrmann and Riemer 2010).

The localization of mutSOD1 in mitochondria likely has a direct role in mitochondrial damage and cell dysfunctions in ALS, because increasing the amount of these proteins in the organelles either by sequence targeting or by overexpression of CCS enhances mitochondrial damage and accelerates motor neuron degeneration (Cozzolino et al. 2009; Magrane et al. 2009; Takeuchi et al. 2002). The noxious mutSOD1 species is most likely the oligomeric form, because toxic phenotypes are prevented when mitochondrial aggregated mutSOD1s are decreased by interfering with their ability to form disulfide-linked oligomers. However, decreasing the amount of such oligomers by introducing a C111S substitution, that has a major role in the formation of disulfide-linked oligomers by mutSOD1s (Cozzolino et al. 2008a; Niwa et al. 2007), neither results in a proportional decrease of mutant SOD1 mitochondrial localization (Kawamata and Manfredi 2008), nor completely abolishes the mitochondrial alterations that are observed in cells overexpressing a mitochondria-targeted mutSOD1 (Cozzolino et al. 2009), suggesting that misfolding of the monomer *by itself* is sufficient to trap SOD1 in mitochondria and to elicit mitochondrial defects. Nonetheless, maneuvers that are able to decrease the amount of mitochondria-aggregated mutSOD1 proved to be effective in protecting cells from mutSOD1-toxicity. As an example, we have recently shown that the overexpression of Glutaredoxin2 (Grx2), a mitochondrial thiol–disulfide oxidoreductase involved in the catalysis of thiol–disulfide interchange reactions, increases the solubility of mutant SOD1 in mitochondria, interferes with mitochondrial fragmentation by modifying the expression pattern of proteins involved in mitochondrial dynamics, preserves mitochondrial function and strongly protects neuronal cells from apoptosis (Ferri et al. 2010).

It is also interesting to notice that common toxic properties have been recently postulated for wild-type SOD1 and mutant

SOD1 (Ezzi et al. 2007). A fraction of wild type SOD1 is physiologically present in a partially *apo*-, copper-free form (Steinkuhler et al. 1991), and recent work demonstrates that *apo*- wild type and mutant SOD1 share an abnormal conformation and a tendency to form oligomers in vitro (Banci et al. 2008). Furthermore, motor neurons in the spinal cord of some sporadic ALS patients (not carrying SOD1 mutations) contain an aberrant wild-type SOD1 species functionally equivalent to mutant SOD1 in its ability to bind an antibody raised against misfolded SOD1 (and thus sharing a conformational epitope that is not present in normal wild-type SOD1) and to inhibit kinesin-based fast axonal transport (Bosco et al. 2010). Thus, that mitochondria-accumulated, oxidized wild-type SOD1 could be pathogenic in sporadic ALS, in analogy to what has been observed for mutSOD1 is possible, although yet to be fully demonstrated.

Altogether, these results strongly indicate that mitochondrial localization of mutSOD1 is per se sufficient to induce mitochondrial alterations, including changes in mitochondrial motility, dynamics and turnover that may lead to neurodegeneration (Chen and Chan 2009). Indeed, in recent years a wealth of data has supported the notion that correct axonal transport and the movement of mitochondria along the axons are impaired in ALS with a depletion of mitochondria from the axons and an accumulation of organelles in clusters along neurites (De Vos et al. 2008; Magrane et al. 2009). Whether these defects stem from a direct disturbance of the transport machinery caused by mutSOD1s or as an effect secondary to insufficient ATP supply remains to be clarified (Magrane et al. 2009).

Mitochondria fusion and fission may also be altered as a consequence of the expression, localization and aggregation of mutSOD1 in mitochondria. The alterations in the morphology of mitochondria that have been frequently described in cellular and animal models of mutSOD1-ALS are highly indicative of mitochondrial fragmentation (Magrane et al. 2009; Martin et al. 2007; Raimondi et al. 2006), and mitochondrial fragmentation is recapitulated in neuronal cells overexpressing a mitochondria-targeted mutSOD1 (Cozzolino et al. 2009). Moreover, we have recently demonstrated that expression of mutSOD1 in neuronal cells is paralleled by alterations in the expression pattern of two proteins that are known to control mitochondria dynamics, i.e. OPA1 (optic atrophy 1), which is a pro-fusion factor, and Drp1 (dynamin-related protein 1), a protein that causes fragmentation when associated with mitochondria (Ferri et al. 2010).

Consequences of mitochondrial damage

Mitochondrial mutSOD1 might affect mitochondrial functions either decreasing protein import selectively in spinal cord mitochondria (Li et al. 2010) as a consequence of its accumulation on the cytoplasmic face of the OM, where the TOM machinery for protein import resides (Liu et al. 2004), or binding and inactivating specific mitochondrial targets such as the voltage-dependent anion channel (VDAC1), an integral membrane protein imbedded in the outer mitochondrial membrane with a protective role on spinal motor neurons (Israelson et al. 2010), the anti-apoptotic protein Bcl-2 (Pedrini et al. 2010) or the mitochondrial form of lysyl-tRNA synthetase (Kawamata and Manfredi 2008).

Besides these target-specific effects, mutSOD1 may affect overall mitochondrial function by increasing the intrinsic load of oxidative stress endured by the organelles.

In conditions like aging, dysfunction of mitochondrial ETC not only causes an energy deficit, but also causes a generalized intracellular oxidative stress (Wei et al. 1998) that is particularly challenging for mitochondria because they are strictly dependent on membrane integrity for function, because many indispensable mitochondrial proteins possess highly oxidizable iron-sulfur clusters and because mitochondrial DNA is more susceptible to mutation than nuclear DNA. There is vast evidence supporting a role for a condition of oxidative stress and mitochondrial dysfunction in ALS, and the impairment of the ETC in patients and in transgenic mice expressing a mutSOD1 gene, where mitochondrial damage is an early sign preceding motor neuron loss, is unquestionable (for a review, see (Cozzolino et al. 2008b). Expression of mutSOD1 is per se able to induce a significant loss of mitochondrial membrane potential, decreased ATP levels and increased production of ROS (Arciello et al. 2010; Beretta et al. 2003; Ferri et al. 2006; Menzies et al. 2002). These effects are accompanied with a shift in the redox balance, as expressed by the ratio between reduced and oxidized glutathione, toward a more oxidizing state in mitochondria (Ferri et al. 2006), and thus it is not entirely surprising that restoring a correct GSH/GSSG ratio through the expression of glutaredoxin 2 restores mitochondrial function in vitro (Ferri et al. 2010).

Mitochondrial damage may have other consequences. Excitotocity from increased intracellular calcium following mis-handling of intersynaptic glutamate has often been considered a major facet of neuron degeneration in ALS. However, it is possible that calcium dysmetabolism in ALS mostly derives by defective intracellular handling (Grosskreutz et al. 2010), since impaired mitochondrial Ca^{2+} buffering in ALS has been repeatedly reported in patients and in cell and animal models for SOD1-linked ALS (Siklos et al. 1996; Carri et al. 1997; Jaiswal et al. 2009; Kruman et al. 1999; Damiano et al. 2006; Jaiswal and Keller 2009). In turn, calcium dysregulation is also strictly interconnected to mitochondrial pathology, oxidative stress and protein aggregation. High Ca^{2+} concentrations induce production of ROS

in mitochondria (Zhou et al. 2010b), rounding of mitochondria, a marked decrease in $\Delta\psi$, increased [Ca^{2+}] in the ER and in the cytosol, and finally the appearance of mutSOD1 inclusions (Dykens 1994).

Both calcium dysregulation and mitochondrial dysfunction regulate apoptosis in the nervous system (Tradewell et al. 2011). Markers of apoptosis such as translocation of Bax from cytosol to mitochondria, release of cytochrome c from mitochondria to cytosol, activation of caspase-9, -3 and −7, inactivation of the inhibitor of apoptosis XIAP and induction of Bcl2A1 have been reported in animal and cell models overexpressing mutSOD1s, and interfering with the apoptotic pathway has some beneficial effects in mutSOD1 mice (Kroemer et al. 2007; Crosio et al. 2006; Guegan et al. 2001; Pasinelli et al. 2000). Mutant SOD1 may have a direct role in the induction of this pathway, since it binds to Bcl-2 and shifts Bcl-2 from an anti-apoptotic to a pro-apoptotic function (Pasinelli et al. 2004; Pedrini et al. 2010).

Finally, an unexpected consequence of mitochondrial damage induced by mutSOD1 is the deregulation of the pattern of transcription and alternative splicing of a subset of mRNAs, including some coding for proteins involved in neuritogenesis and axon guidance (Lenzken et al. 2011). This observation may help linking the more frequent case of SOD1-linked familial ALS and the familial ALS phenotype observed in patients carrying mutations in one of the two RNA binding proteins TDP43 and FUS (Kabashi et al. 2008). Some recent work provides evidence of mitochondrial damage in experimental models or patients with mutation in one of these two proteins (Huang et al. 2010; Shan et al. 2010; Xu et al. 2010), but whether also mutant TDP-43 and FUS/TLS are linked directly or indirectly to mitochondrial damage is still to be ascertained.

Concluding remarks

The wealth of evidence on mitochondrial dysfunction in ALS has prompted studies aimed to the development of mitochondria-targeted therapies. However, a number of attempts to restore correct function of these organelles that were successful in models in vivo and in vitro (e.g. treatment with a number of different antioxidants or mitochondrial modulators, such as creatine) have failed to translate into clinical practice (Cozzolino and Carrì 2011). This may be due to the choice of the wrong mitochondrial target, and current studies are aimed to the development of new approaches, such as the modulation of the mitochondrial dynamics, the intracellular calcium handling or the opening of the mitochondrial Permeability Transition Pore (Martin et al. 2009), that appears to be particularly relevant in adult-onset neurodegenerative diseases (Toman and Fiskum 2011). Alternatively, previous studies (and failures) may reinforce the idea that since ALS is a multi-factorial, multi-systemic disease, no single treatment may be successful and we should look for a combined therapy. Along this line of research, some recent studies are aimed at testing drugs that act both as mitochondrial modulators and anti-inflammatories or antiglutamatergics, or that exert a broad spectrum of neuroprotective properties, such as antioxidant effects, inhibition of apoptotic enzymes and preservation of mitochondrial structure and activity (Cheah and Kiernan 2010). These approaches will hopefully provide new routes for the treatment of this fatal disease.

Acknowledgments MTC's research is supported by grants from ALS Association, Telethon, MIUR (PRIN), IMI-San Paolo, Fondation Thierry-Latran, ERA-Net Neuron; MC's research is supported by Association Française contre les Myopathies and by AriSLA.

References

Aquilano K, Vigilanza P, Rotilio G, Ciriolo MR (2006) FASEB J 20:1683–1685
Arciello M, Capo CR, Cozzolino M, Ferri A, Nencini M, Carri MT, Rossi L (2010) J Neurochem 112:183–192
Banci L, Bertini I, Boca M, Girotto S, Martinelli M, Valentine JS, Vieru M (2008) PLoS One 3:e1677
Bendotti C, Carri MT (2004) Trends Mol Med 10:393–400
Beretta S, Sala G, Mattavelli L, Ceresa C, Casciati A, Ferri A, Carri MT, Ferrarese C (2003) Neurobiol Dis 13:213–221
Bergemalm D, Jonsson PA, Graffmo KS, Andersen PM, Brannstrom T, Rehnmark A, Marklund SL (2006) J Neurosci 26:4147–4154
Bosco DA, Morfini G, Karabacak NM, Song Y, Gros-Louis F, Pasinelli P, Goolsby H, Fontaine BA, Lemay N, McKenna-Yasek D, Frosch MP, Agar JN, Julien JP, Brady ST, Brown RH Jr (2010) Nat Neurosci 13:1396–1403
Carri MT, Ferri A, Battistoni A, Famhy L, Gabbianelli R, Poccia F, Rotilio G (1997) FEBS Lett 414:365–368
Carri MT, Grignaschi G, Bendotti C (2006) Trends Pharmacol Sci 27:267–273
Cheah BC, Kiernan MC (2010) IDrugs 13:911–920
Chen H, Chan DC (2009) Hum Mol Genet 18:R169–R176
Cozzolino M, Amori I, Pesaresi MG, Ferri A, Nencini M, Carri MT (2008a) J Biol Chem 283:866–874
Cozzolino M, Ferri A, Carri MT (2008b) Antioxid Redox Signal 10:405–443
Cozzolino M, Pesaresi MG, Amori I, Crosio C, Ferri A, Nencini M, Carri MT (2009) Antioxid Redox Signal 11:1547–1558
Cozzolino M, Carrì MT (2011) Prog Neurobiol. doi: 10.1016/j.pneurobio.2011.06.003
Crosio C, Casciati A, Iaccarino C, Rotilio G, Carri MT (2006) Cell Death Differ 13:2150–2153
Damiano M, Starkov AA, Petri S, Kipiani K, Kiaei M, Mattiazzi M, Flint Beal M, Manfredi G (2006) J Neurochem 96:1349–1361
De Vos KJ, Grierson AJ, Ackerley S, Miller CC (2008) Annu Rev Neurosci 31:151–173
Deas E, Wood NW, Plun-Favreau H (2011) Biochim Biophys Acta 1813:623–633
Deng HX, Shi Y, Furukawa Y, Zhai H, Fu R, Liu E, Gorrie GH, Khan MS, Hung WY, Bigio EH, Lukas T, Dal Canto MC,

O'Halloran TV, Siddique T (2006) Proc Natl Acad Sci U S A 103:7142–7147
Dykens JA (1994) J Neurochem 63:584–591
Ezzi SA, Urushitani M, Julien JP (2007) J Neurochem
Ferri A, Fiorenzo P, Nencini M, Cozzolino M, Pesaresi MG, Valle C, Sepe S, Moreno S, Carri MT. Hum Mol Genet 19:4529–4542
Ferri A, Cozzolino M, Crosio C, Nencini M, Casciati A, Gralla EB, Rotilio G, Valentine JS, Carri MT (2006) Proc Natl Acad Sci U S A 103:13860–13865
Ferri A, Fiorenzo P, Nencini M, Cozzolino M, Pesaresi MG, Valle C, Sepe S, Moreno S, Carri MT (2010) Hum Mol Genet 19:4529–4542
Field LS, Furukawa Y, O'Halloran TV, Culotta VC (2003) J Biol Chem 278:28052–28059
Fischer LR, Igoudjil A, Magrane J, Li Y, Hansen JM, Manfredi G, Glass JD (2011) Brain 134:196–209
Furukawa Y, Fu R, Deng HX, Siddique T, O'Halloran TV (2006) Proc Natl Acad Sci U S A 103:7148–7153
Grosskreutz J, Van Den Bosch L, Keller BU (2010) Cell Calcium 47:165–174
Guegan C, Vila M, Rosoklija G, Hays AP, Przedborski S (2001) J Neurosci 21:6569–6576
Herrmann JM, Riemer J (2010) Antioxid Redox Signal 13:1341–1358
Higgins CM, Jung C, Ding H, Xu Z (2002) J Neurosci 22:RC215
Huang EJ, Zhang J, Geser F, Trojanowski JQ, Strober JB, Dickson DW, Brown RH Jr, Shapiro BE, Lomen-Hoerth C (2010) Brain Pathol 20:1069–1076
Ilieva H, Polymenidou M, Cleveland DW (2009) J Cell Biol 187:761–772
Israelson A, Arbel N, Da Cruz S, Ilieva H, Yamanaka K, Shoshan-Barmatz V, Cleveland DW (2010) Neuron 67:575–587
Jaarsma D, Rognoni F, van Duijn W, Verspaget HW, Haasdijk ED, Holstege JC (2001) Acta Neuropathol (Berl) 102:293–305
Jaiswal MK, Keller BU (2009) Mol Pharmacol 75:478–489
Jaiswal MK, Zech WD, Goos M, Leutbecher C, Ferri A, Zippelius A, Carri MT, Nau R, Keller BU (2009) BMC Neurosci 10:64
Kabashi E, Valdmanis PN, Dion P, Spiegelman D, McConkey BJ, Vande Velde C, Bouchard JP, Lacomblez L, Pochigaeva K, Salachas F, Pradat PF, Camu W, Meininger V, Dupre N, Rouleau GA (2008) Nat Genet 40:572–574
Kawamata H, Manfredi G (2008) Hum Mol Genet 17:3303–3317
Kiernan MC, Vucic S, Cheah BC, Turner MR, Eisen A, Hardiman O, Burrell JR, Zoing MC (2011) Lancet 377:942–955
Kloppel C, Michels C, Zimmer J, Herrmann JM, Riemer J (2010) Biochem Biophys Res Commun 403:114–119
Kroemer G, Galluzzi L, Brenner C (2007) Physiol Rev 87:99–163
Kruman II, Pedersen WA, Springer JE, Mattson MP (1999) Exp Neurol 160:28–39
Lenzken SC, Romeo V, Zolezzi F, Cordero F, Lamorte G, Bonanno D, Biancolini D, Cozzolino M, Pesaresi MG, Maracchioni A, Sanges R, Achsel T, Carri MT, Calogero RA, Barabino SM (2011) Hum Mutat 32:168–182
Li Q, Vande Velde C, Israelson A, Xie J, Bailey AO, Dong MQ, Chun SJ, Roy T, Winer L, Yates JR, Capaldi RA, Cleveland DW, Miller TM (2010) Proc Natl Acad Sci U S A 107:21146–21151
Liu J, Lillo C, Jonsson PA, Vande Velde C, Ward CM, Miller TM, Subramaniam JR, Rothstein JD, Marklund S, Andersen PM, Brannstrom T, Gredal O, Wong PC, Williams DS, Cleveland DW (2004) Neuron 43:5–17
Magrane J, Manfredi G (2009) Antioxid Redox Signal 11:1615–1626
Magrane J, Hervias I, Henning MS, Damiano M, Kawamata H, Manfredi G (2009) Hum Mol Genet 18:4552–4564
Martin LJ, Liu Z, Chen K, Price AC, Pan Y, Swaby JA, Golden WC (2007) J Comp Neurol 500:20–46
Martin LJ, Gertz B, Pan Y, Price AC, Molkentin JD, Chang Q (2009) Exp Neurol 218:333–346
Mattiazzi M, D'Aurelio M, Gajewski CD, Martushova K, Kiaei M, Beal MF, Manfredi G (2002) J Biol Chem 277:29626–29633
McCord JM, Fridovich I (1969) J Biol Chem 244:6049–6055
Menzies FM, Cookson MR, Taylor RW, Turnbull DM, Chrzanowska-Lightowlers ZM, Dong L, Figlewicz DA, Shaw PJ (2002) Brain 125:1522–1533
Morimoto N, Nagai M, Ohta Y, Miyazaki K, Kurata T, Morimoto M, Murakami T, Takehisa Y, Ikeda Y, Kamiya T, Abe K (2007) Brain Res 1167:112–117
Morimoto N, Nagai M, Miyazaki K, Ohta Y, Kurata T, Takehisa Y, Ikeda Y, Matsuura T, Asanuma M, Abe K (2010) J Neurosci Res 88:1804–1811
Niwa J, Yamada S, Ishigaki S, Sone J, Takahashi M, Katsuno M, Tanaka F, Doyu M, Sobue G (2007) J Biol Chem 282:28087–28095
O'Brien KM, Dirmeier R, Engle M, Poyton RO (2004) J Biol Chem 279:51817–51827
Okado-Matsumoto A, Fridovich I (2001) J Biol Chem 276:38388–38393
Okamoto K, Hirai S, Shoji M, Senoh Y, Yamazaki T (1990) Acta Neuropathol 80:222–226
Pasinelli P, Houseweart MK, Brown RH Jr, Cleveland DW (2000) Proc Natl Acad Sci U S A 97:13901–13906
Pasinelli P, Belford ME, Lennon N, Bacskai BJ, Hyman BT, Trotti D, Brown RH Jr (2004) Neuron 43:19–30
Pedrini S, Sau D, Guareschi S, Bogush M, Brown RH Jr, Naniche N, Kia A, Trotti D, Pasinelli P (2010) Hum Mol Genet 19:2974–2986
Pizzasegola C, Caron I, Daleno C, Ronchi A, Minoia C, Carri MT, Bendotti C (2009) Amyotroph Lateral Scler 10:221–228
Raimondi A, Mangolini A, Rizzardini M, Tartari S, Massari S, Bendotti C, Francolini M, Borgese N, Cantoni L, Pietrini G (2006) Eur J Neurosci 24:387–399
Reddehase S, Grumbt B, Neupert W, Hell K (2009) J Mol Biol 385:331–338
Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, Donaldson D, Goto J, O'Regan JP, Deng HX et al (1993) Nature 362:59–62
Schmidt O, Pfanner N, Meisinger C (2010) Nat Rev Mol Cell Biol 11:655–667
Shan X, Chiang PM, Price DL, Wong PC (2010) Proc Natl Acad Sci U S A 107:16325–16330
Shi P, Gal J, Kwinter DM, Liu X, Zhu H (2010a) Biochim Biophys Acta 1802:45–51
Shi P, Wei Y, Zhang J, Gal J, Zhu H (2010b) J Alzheimers Dis 20 (Suppl 2):S311–S324
Siklos L, Engelhardt J, Harati Y, Smith RG, Joo F, Appel SH (1996) Ann Neurol 39:203–216
Sreedharan J, Blair IP, Tripathi VB, Hu X, Vance C, Rogelj B, Ackerley S, Durnall JC, Williams KL, Buratti E, Baralle F, de Belleroche J, Mitchell JD, Leigh PN, Al-Chalabi A, Miller CC, Nicholson G, Shaw CE (2008) Science 319:1668–1672
Steinkuhler C, Sapora O, Carri MT, Nagel W, Marcocci L, Ciriolo MR, Weser U, Rotilio G (1991) J Biol Chem 266:24580–24587
Takeuchi H, Kobayashi Y, Ishigaki S, Doyu M, Sobue G (2002) J Biol Chem 277:50966–50972
Toman J, Fiskum G (2011) J Bioenerg Biomembr 43:3–10
Tradewell ML, Cooper LA, Minotti S, Durham HD (2011) Neurobiol Dis 42:265–275
Vance C, Rogelj B, Hortobagyi T, De Vos KJ, Nishimura AL, Sreedharan J, Hu X, Smith B, Ruddy D, Wright P et al (2009) Science 323:1208–1211
Vande Velde C, Miller TM, Cashman NR, Cleveland DW (2008) Proc Natl Acad Sci U S A 105:4022–4027
Vijayvergiya C, Beal MF, Buck J, Manfredi G (2005) J Neurosci 25:2463–2470
Wei YH, Lu CY, Lee HC, Pang CY, Ma YS (1998) Ann N Y Acad Sci 854:155–170
Weisiger RA, Fridovich I (1973) J Biol Chem 248:4793–4796

Xu YF, Gendron TF, Zhang YJ, Lin WL, D'Alton S, Sheng H, Casey MC, Tong J, Knight J, Yu X, Rademakers R, Boylan K, Hutton M, McGowan E, Dickson DW, Lewis J, Petrucelli L (2010) J Neurosci 30:10851–10859

Zhou H, Huang C, Chen H, Wang D, Landel CP, Xia PY, Bowser R, Liu YJ, Xia XG (2010a) PLoS Genet 6:e1000887

Zhou J, Yi J, Fu R, Liu E, Siddique T, Rios E, Deng HX (2010b) J Biol Chem 285:705–712