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MINI REVIEW

Mitochondrial dysfunction in familial amyotrophic lateral sclerosis

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Abstract A growing body of evidence suggests that mitochondrial dysfunctions play a crucial role in the pathogenesis of various neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS), a neurodegenerative disease affecting both upper and lower motor neurons. Although ALS is predominantly a sporadic disease, approximately 10% of cases are familial. The most frequent familial form is caused by mutations in the gene encoding Cu/Zn superoxide dismutase 1 (SOD1). A dominant toxic gain of function of mutant SOD1 has been considered as the cause of the disease and mitochondria are thought to be key players in the pathogenesis. However, the exact nature of the link between mutant SOD1 and mitochondrial dysfunctions remains to be established. Here, we briefly review the evidence for mitochondrial dysfunctions in familial ALS and discuss a possible link between mutant SOD1 and mitochondrial dysfunction.

Keywords Amyotrophic lateral sclerosis · Neurodegeneration · Mitochondria · Mutant SOD1

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive disease characterized by the loss of upper and lower motor neurons. In most ALS cases there is no clear genetic linkage (sporadic ALS) but in approximately 10% of ALS patients the disease is inherited (familial ALS). About 20% of these familial ALS cases are caused by autosomal dominant mutations in the gene encoding Cu/Zn superoxide dismutase 1 (SOD1) (Rosen et al. 1993; reviewed in Cleveland and Rothstein 2001; Pasinelli and Brown 2006; Turner and Talbot 2008). This enzyme mediates the conversion of superoxide anions, mainly generated during oxidative phosphorylation, into hydrogen peroxide, an indispensible defense mechanism against reactive oxygen species (ROS). To date, over 140 different mutations in the SOD1 gene have been identified (http://alsod.iop.kcl.ac.uk/Als/Summary/summary.aspx). Since loss of SOD1 activity does not always result from these mutations (Borchelt et al. 1994; Bowling et al. 1995) and SOD1 knockout mice show no overt motor deficits (Reaume et al. 1996), it is now widely accepted that these mutations cause SOD1 to gain a toxic property. Several mechanisms for this toxicity have been proposed including mitochondrial dysfunctions, oxidative stress, Ca^{2+} dysregulation, aggregation of aberrantly processed proteins, endoplasmic reticulum (ER) stress, axonal transport disruption, glutamate excitotoxicity, apoptosis and inflammation (reviewed in Barber and Shaw 2010; Boillee et al. 2006; Duffy et al. 2011; Grosskreutz et al. 2010; Hervias et al. 2006; Manfredi and Xu 2005). The pathogenicity of SOD1 mutations therefore appears to reflect a combination of different mechanisms acting together or consecutively and ultimately leading to cell death. Dissecting out the relative significance of each mechanism remains challenging. Here, we briefly review mitochondrial dysfunction as a possible determining factor in the pathogenesis of familial ALS.

Mitochondrial morphological abnormalities and dysfunctions in familial ALS

Mitochondrial functions can be directly or indirectly linked to most, if not all, of the postulated causal mechanisms

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involved in ALS including dysregulation of intracellular Ca^{2+} homeostasis, oxidative stress, glutamate excitotoxicity, apoptosis and axonal transport disruption. Therefore, mitochondria can be considered as a convergence point in motor neuron degeneration. Mitochondrial damage has been well documented in both sporadic and familial ALS. The first evidence of mitochondrial abnormalities came from ultrastructural studies showing aggregates of mitochondria in muscles and spinal cord motor neurons (Sasaki and Iwata 1996) and increased mitochondrial volume in motor nerve terminals of ALS patients (Siklos et al. 1996). Consistent with these findings, observations of mitochondrial morphology in cell or animal models of familial ALS showed aggregated, swollen, vacuolated or fragmented mitochondria (Bendotti et al. 2001; Coussee et al. 2011; Damiano et al. 2006; Jaarsma et al. 2001; Jung et al. 2002; Menzies et al. 2002; Raimondi et al. 2006; Xu et al. 2004).

Several lines of evidence further indicate that these mitochondrial morphology changes are tightly associated with mitochondrial dysfunctions. Changes in the activity of the different complexes of the electron transport chain have been described in tissues obtained from ALS patients, and in cell and animal disease models. Although some of these studies have produced mixed and somewhat contradictory results, the most consistent abnormality in mitochondrial respiratory function has been associated with reduced complex I and IV activity (Browne et al. 1998; Kirkinezos et al. 2005; Mattiazzi et al. 2002; Menzies et al. 2002; Rizzardini et al. 2006; Son et al. 2008). In motor neurons of mutant $SOD1^{G93A}$ mice a reduction in activity of complex I was observed before disease onset and progressing to inhibition of complex IV at later stages (Jung et al. 2002). In neuroblastoma cells overexpressing mutant $SOD1^{G37R}$, we observed a decreased activity of complex I in mitochondrial fractions (Coussee et al. 2011). This reduction was not related to a lower expression level of complex I.

The maintenance of the mitochondrial membrane potential is reliant on the activity of the different complexes of the electron transport chain. Consistent with this, mitochondrial depolarization has been observed in neuroblastoma cells expressing mutant $SOD1^{G93A}$ (Carri et al. 1997) or $SOD1^{G37R}$ (Coussee et al. 2011) and in motor neurons from mutant $SOD1^{G93A}$ mice (Kruman et al. 1999). Stimulation-induced mitochondrial membrane depolarizations in motor terminals of G93A and G85R transgenic mice were significantly enhanced and increased the likelihood of mitochondrial permeability transition pore opening during mitochondrial Ca^{2+} uptake (Nguyen et al. 2011; Nguyen et al. 2009).

Another set of observations, providing further evidence for mitochondrial dysfunctions in the pathogenesis of familial ALS include impaired ATP synthesis and reduced mitochondrial Ca^{2+} buffering in cells expressing a number of different SOD1 mutations. For example, ATP generation was markedly decreased in neuronal cells of mutant $SOD1^{G93A}$ mice (Browne et al. 2006; Mattiazzi et al. 2002). Cytosolic ATP levels were significantly reduced in neuroblastoma cells expressing mutant $SOD1^{G37R}$ (Coussee et al. 2011) and decreased more rapidly and to a greater extent in rotenone-treated $SOD1^{G93A}$ neuronal cells (Rizzardini et al. 2006). Impairment of intracellular Ca^{2+} homeostasis has been reported in cells expressing mutant $SOD1^{G93A}$ or $SOD1^{G37R}$ (Carri et al. 1997; Coussee et al. 2011; Tradewell et al. 2011) and in motor neurons from mutant $SOD1^{G93A}$ transgenic mice (Jaiswal and Keller 2009; Jaiswal et al. 2009; Kruman et al. 1999). Also isolated mitochondria from transgenic mutant $SOD1^{G93A}$ and $SOD1^{G85R}$ mice showed a significant decrease in Ca^{2+} loading capacity (Damiano et al. 2006; Nguyen et al. 2009; Vila et al. 2003). ATP deficit and Ca^{2+} dysregulation may arise secondary to mutant SOD1-induced impairment of oxidative phosphorylation, or as a direct consequence of mutant SOD1 impeding on mitochondrial transport of ions and metabolites.

Finally, numerous studies have found evidence of increased oxidative and/or nitrosative stress in ALS pathogenesis. Transgenic mouse models of ALS expressing mutant human SOD1 support human studies showing increased oxidative damage to mitochondrial proteins, lipids and DNA (reviewed in Barber and Shaw 2010). This has been explained by excessive dismutase activity of mutant SOD1 (Goldsteins et al. 2008; Wiedau-Pazos et al. 1996), increased levels of ROS produced by mitochondria following inhibition of complex I (Kruman et al. 1999; Mattiazzi et al. 2002; Murphy 2009; Zimmerman et al. 2007), or increased NADPH oxidase (NOX) activity through mutant SOD1 interacting with Rac1, a NOX regulator (reviewed in Boillee and Cleveland 2008). It should be noted, however, that recent data indicate that overexpression of mutant $SOD1^{G93A}$ in yeast cells actually provided increased protection against respiration-derived ROS (Kloppel et al. 2010).

Despite the clear evidence that mutant SOD1 induces a fundamental impairment in energy metabolism mechanisms, Ca^{2+} homeostasis and ROS handling, the exact cause and effect remain unclear. A number of potential scenarios exist. Of particular interest is the observation that mutant SOD1 preferentially accumulates at the cytoplasmic face of the outer membrane and in the intermembrane space of mitochondria (Cozzolino et al. 2009; Ferri et al. 2006; Higgins et al. 2003; Sotelo-Silveira et al. 2009). Therefore, it is possible that an aberrant association between mutant SOD1 and mitochondrial proteins may lead to impaired electron transport chain functioning, shortage of ATP, increased ROS formation and Ca^{2+} dysregulation.

Mutant SOD1 may affect ER-mitochondrial coupling

One way how mislocalized mutant SOD1 could affect mitochondrial functions is through direct interaction with outer mitochondrial membrane proteins. Mutant SOD1 has been shown to associate with Lysyl-tRNA synthetase (Kawamata et al. 2008), an enzyme required for mitDNA-encoded protein translation, members of the Bcl-2 family of proteins (Arbel and Shoshan-Barmatz 2010) and the voltage-dependent anion channel VDAC1 (Israelson et al. 2010). The binding of mutant SOD1 to VDAC1 deserves further attention. VDAC1 is a multifunctional mitochondrial protein involved in the transport of ions and small molecules including Ca^{2+}, ATP/ADP and NADH, across the mitochondrial outer membrane (reviewed in Colombini 2004; Pedersen 2008; Shoshan-Barmatz and Ben-Hail 2011; Shoshan-Barmatz et al. 2010). Changes in the transport rate of these ions and molecules will affect mitochondrial and cellular metabolism, positioning VDAC1 at a key position in the cellular energy metabolism. VDAC1 has also been found in ER membrane fractions, notably at contact sites between mitochondria and ER, where it may catalyze the uptake of ATP (Shoshan-Barmatz and Israelson 2005). In addition to its key role in energy metabolism, VDAC1 also binds to pro- and anti-apoptotic proteins of the Bcl-2 family, is an essential component of the permeability transition pore and has therefore been proposed to be a key player in mitochondria-mediated apoptosis (reviewed in Shoshan-Barmatz and Ben-Hail 2011; Shoshan-Barmatz et al. 2010). Furthermore, VDAC1 interacts with several other mitochondrial and cytosolic proteins and recent evidence indicates that it may be part of the physical link between mitochondria and the ER Ca^{2+}-release channel inositol 1,4,5-trisphosphate receptor (IP_3R) (Szabadkai et al. 2006). This tight coupling between ER and mitochondria through IP_3R-VDAC1 associations not only allows VDAC1-mediated Ca^{2+} fluxes to the intermembrane space from the high [Ca^{2+}] microdomain created by activation of IP_3Rs but also provides high [ATP] microdomains required for subsequent SERCA-mediated Ca^{2+} reuptake into the ER. It thus seems obvious that even small changes in the number or distance of these physical contacts between mitochondria and ER may have profound effects on mitochondrial and cellular functions. A decrease in the number of physical contacts between mitochondria and ER or an increase in their distance would diminish mitochondrial Ca^{2+} uptake induced by IP_3-mediated Ca^{2+} release. Since mitochondrial oxidative phosphorylation is stimulated at different levels (three dehydrogenases of the Krebs cycle and the F_1F_0 ATP synthase) by Ca^{2+} (Jouaville et al. 1999), reduced mitochondrial Ca^{2+} uptake would impede ATP production. For the same reasons, ER-mitochondrial uncoupling would limit the generation of [ATP] hot spots. In addition, the recent finding that mutant SOD1 binding to VDAC1 reduces VDAC1-mediated ADP transport across the outer mitochondrial membrane (Israelson et al. 2010) will further limit ATP synthesis. In all these cases, ATP generation may thus be seriously hampered that it actually falls short of cytosolic ATP demand during on-going cellular activity. Since VDAC1 plays a central role in cellular metabolism and serves as a mitochondrial-binding site for other proteins, including mutant SOD1 and IP_3Rs, an appealing hypothesis is that this aberrant interaction of mutant SOD1 with VDAC1 not only impairs VDAC1-mediated transport across the mitochondrial outer membrane

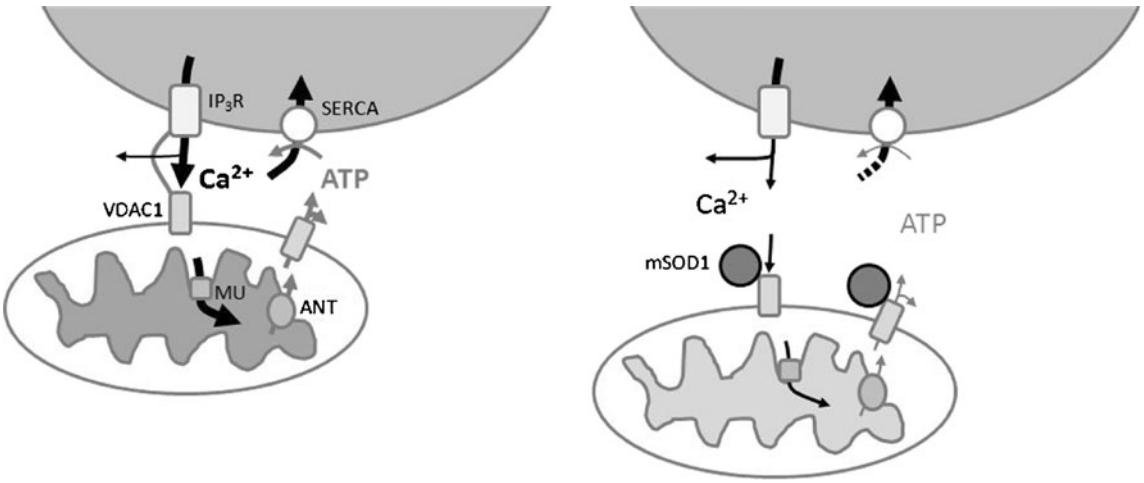

Fig. 1 Simplified model for altered mitochondrial Ca^{2+} uptake and ATP production in mutant SOD1 cells. Binding of mutant SOD1 (mSOD1) to VDAC1 results in uncoupling of ER/mitochondrial network leading to diminished mitochondrial Ca^{2+} uptake, increased cytosolic Ca^{2+} transient and lower ATP availability. Dark grey level corresponds to high Ca^{2+} content; thick black arrows reflect high Ca^{2+} flux; thick grey arrows reflect high ATP flux. MU mitochondrial uniporter; ANT adenine nucleotide transporter

but also destabilizes VDAC1 binding to IP_3Rs. This leads to a reduction of the number of VDAC1 proteins available for IP_3R coupling and hence impairing the privileged communication between mitochondria and ER (Fig. 1).

Consistent with this hypothesis, our own findings in N2a neuroblastoma cells overexpressing mutant $SOD1^{G37R}$ showed decreased IP_3-induced mitochondrial Ca^{2+} uptake in intact cells compared to parental cells (Coussee et al. 2011). IP_3-induced mitochondrial Ca^{2+} uptake was not affected in cells overexpressing wild-type SOD1. Ca^{2+}-induced mitochondrial Ca^{2+} uptake in permeabilized cells, which does not rely on ER Ca^{2+} release or the intimate coupling between mitochondria and ER, was not affected in mutant $SOD1^{G37R}$ cells. This finding is also consistent with the observation that mutant SOD1 does not affect VDAC1-mediated Ca^{2+} transfer (Israelson et al. 2010). Cytosolic ATP levels were also significantly decreased in mutant $SOD1^{G37R}$ cells resulting in compromised ER Ca^{2+} uptake in intact cells while ER Ca^{2+} uptake in permeabilized cells provided with sufficient amounts of ATP was not affected. Our finding that complex I activity is significantly impaired in mutant $SOD1^{G37R}$ cells may reflect reduced VDAC1 permeability for metabolites necessary for respiration. Finally, using confocal microscopy, we compared the distribution of the ER marker Dsred with that of the mitochondrial marker mit-GFP. A quantitative analysis of colocalization between the two signals revealed a lower Mander's coefficient (Mc) in mutant $SOD1^{G37R}$ cells (Mc of 0.64) compared to wild-type SOD1 cells (Mc of 0.56) (unpublished preliminary data). These results suggest a loss of coupling between mitochondria and ER in mutant $SOD1^{G37R}$ cells. Further studies will be needed to corroborate these findings by quantifying Ca^{2+} hot spots or assessing VDAC1 localization at ER-mitochondria contact sites in mutant $SOD1^{G37R}$ cells.

Because mitochondrial Ca^{2+} uptake during IP_3-induced Ca^{2+} release was significantly reduced in mutant $SOD1^{G37R}$ cells, IP_3-induced Ca^{2+} release led to significant larger cytosolic Ca^{2+} signals. Since mutant $SOD1^{G37R}$ expression had no major effects on the viability of N2a neuroblastoma cells, the extrapolation of these findings to motor neuron degeneration appears trivial. However, unlike many other cell types, motor neurons display low cytosolic Ca^{2+} buffering (Grosskreutz et al. 2007; von Lewinski et al. 2008) and heavily rely on oxidative phosphorylation during on-going rhythmic activity. It therefore becomes apparent that cytosolic Ca^{2+} overloading and ATP shortage in motor neurons carrying SOD1 mutations are predominant and pose a sustained metabolic stress on mitochondria, accelerating cellular ageing and ultimately lowering the threshold for apoptosis.

In summary, the aberrant interaction of mutant SOD1 with VDAC1 may impair VDAC1-mediated transport and ER-mitochondria coupling resulting in decreased mitochondrial Ca^{2+} uptake and ATP production. This Ca^{2+} dysregulation and energetic deficit may represent the starting point for a vicious circle leading to motor neuron degeneration in familial ALS.

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