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Mitochondria and ALS: Implications from novel genes and pathways

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ABSTRACT

Evidence from patients with sporadic and familiar amyotrophic lateral sclerosis (ALS) and from models based on the overexpression of mutant SOD1 found in a small subset of patients, clearly point to mitochondrial damage as a relevant facet of this neurodegenerative condition. In this mini-review we provide a brief update on the subject in the light of newly discovered genes (such as TDP-43 and FUS/TLS) associated to familial ALS and of a deeper knowledge of the mechanisms of derangement of mitochondria. This article is part of a Special Issue entitled 'Mitochondrial function and dysfunction in neurodegeneration'.

Mitochondria, ALS and mutant SOD1

Since the first reports of mitochondrial abnormalities in tissues from patients with amyotrophic lateral sclerosis (ALS) (Afifi et al., 1966; Atsumi, 1981; Hart et al., 1977; Okamoto et al., 1990; Siklos et al., 1996), mitochondrial dysfunction has been steadily recognized as a central matter in the pathogenesis of this disease. All aspects of mitochondrial physiology have been analyzed in patients and models based on the expression of mutant SOD1s (mutSOD1) found in a subset of patients, and nearly all have been found to be variably compromised in this pathological condition. The notion that alterations in mitochondrial bioenergetics, clearance of dys-functional organelles, calcium buffering and induction of mitochondrial apoptosis are all important features of the disease has robust foundation deriving from different experimental evidence (Fig. 1) (Duffy et al., 2011). More recently, alterations in mitochondrial morphology, fusion/fission dynamics and biogenesis have attracted much attention, given the importance of such alterations in the overall homeostasis of mitochondrial function (Chen and Chan, 2009). That mitochondrial dynamics may play a relevant role in ALS was put forward by the observation of morphological alterations that are reminiscent of fragmentation in mitochondria of cultured cells and mice expressing mutSOD1 (Cozzolino et al., 2009; Magrane et al., 2009; Vande Velde et al., 2011). Changes in the expression of proteins controlling mitochondrial fusion/fission have also been observed in a cellular model of the disease (Ferri et al., 2010). More recently, using live imaging microscopy, Magranè et al. were able to follow mitochondria reshaping occurring in mutSOD1 expressing motor neurons by virtue of a mitochondria targeted fluorescent probe, and from this analysis they were able to conclude that mitochondrial dynamics alterations and bioenergetic dysfunctions work together in triggering synaptic alterations in motor neurons expressing mutSOD1 (Magrane et al., 2012). Thus, impaired mitochondrial dynamics may have a primary role in the degeneration of motor neurons.

Defective mitochondrial transportation along axons has also been repeatedly proposed to contribute to motor neuron degeneration in ALS models (Bilsland et al., 2010; De Vos et al., 2007; Morotz et al., 2012). However, this hypothesis has been questioned since increasing axonal mitochondrial mobility through genetic ablation of syntaphilin does not affect the onset of ALS-like symptoms in G93A-SOD1 mice (Zhu and Sheng, 2011) and in a recent paper Marinkovic et al. reported that axon degeneration is a much later event than defects in mitochondrial transport in G93A-SOD1 mice. Furthermore, transport deficits do not take place in the G85R-SOD1 model and are insufficient to cause motor neuron death in mice overexpressing wild type SOD1 (Marinkovic et al., 2012). In the case of familial ALS associated with mutSOD1, in the last years much effort has been put to discern whether association of mutant SOD1 to mitochondria is a leading mechanism driving mitochondrial dysfunction. Indeed, a small fraction of wild type SOD1 is normally localized in mitochondria, with an apparent role in preventing oxidative damage in the mitochondrial intermembrane space, a function that seems to be important for motor

Abbreviations: ALS, Amyotrophic Lateral Sclerosis; CFP, Cyan Fluorescent Protein; ER, Endoplasmic Reticulum; FUS/TLS, Fused in Sarcoma/Translocated in Liposarcoma; GSH, Glutathione; HAT, Histone Acetyl Transferase; HDAC, Histone Deacetylase; ROS, Reactive Oxygen Species: SIRT, Sirtuin; SOD1, Cu, Zn Superoxide Dismutase; TDP-43, TAR DNA Binding Protein 43; UPR, Unfolded Protein Response; VAPB, VAMP Associated Protein.

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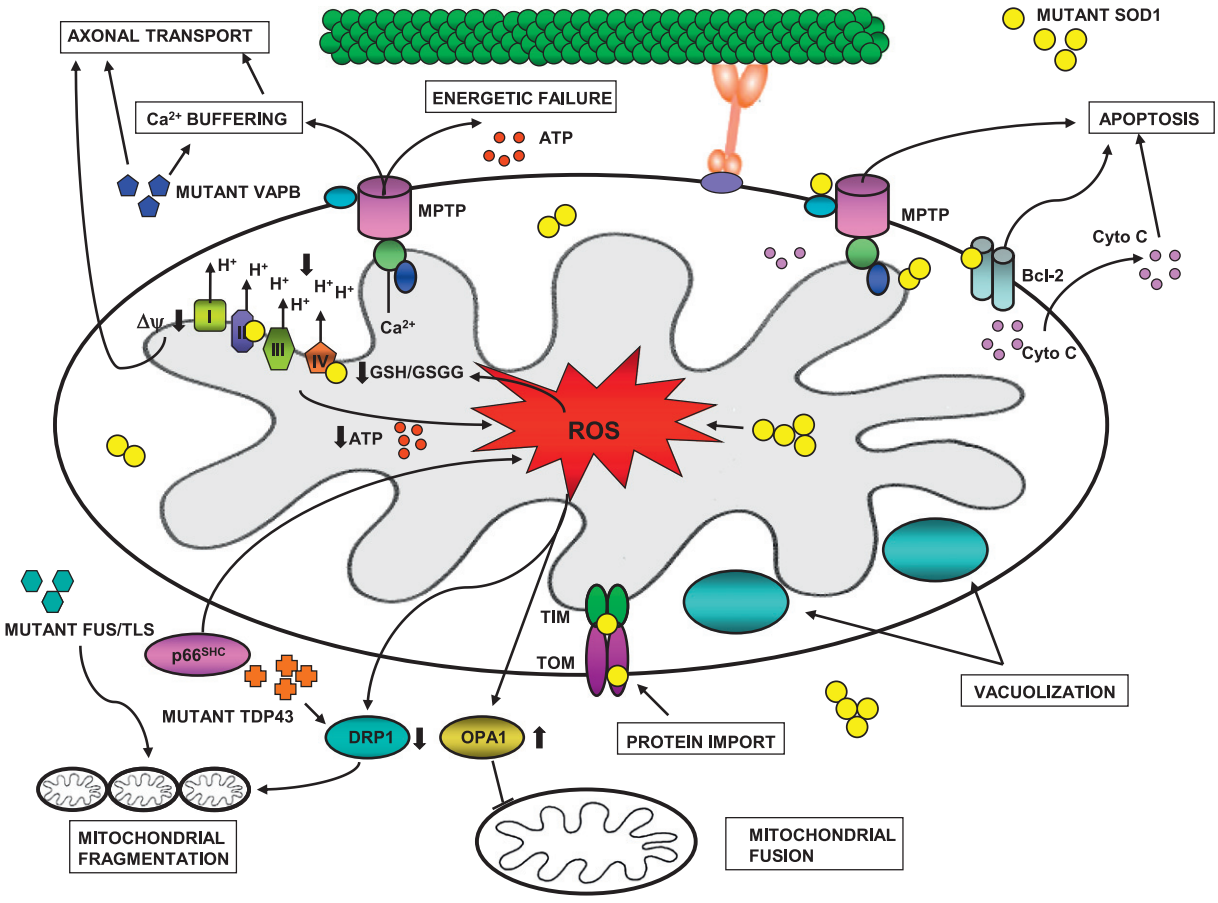

Fig. 1. Mitochondrial dysfunction in Amyotrophic Lateral Sclerosis: causes and consequences. Mutant SOD1 is imported into mitochondria and may interfere with different mitochondrial components. These include the mitochondrial apoptotic machinery, e.g. Bcl-2 (Pasinelli et al., 2004) and MPTP (Martin et al., 2009), triggering cytochrome c release in the cytosol and activation of the apoptotic cascade (Pasinelli et al., 2000); the protein import machinery (Li et al., 2010); the mitochondrial redox balance (GSH/GSSH ratio) (Ferri et al., 2006); cytosolic calcium buffering (Grosskreutz et al., 2010); mitochondrial axonal transport (De Vos et al., 2007); mitochondrial redox signalling by $p66^{shc}$ (Pesaresi et al., 2011); respiratory chain and oxidative phosphorylation (Mattiazzi et al., 2002); membrane potential (Carri et al., 1997; Wiedemann et al., 2002); mitochondrial dynamics (expression DRP1 and OPA1) (Ferri et al., 2010). Abnormal mitochondrial dynamics and fragmentation was observed also in some TDP-43 and FUS/TLS models (Tradewell et al., 2012; Xu et al., 2010). Mutant VAPB may alter maintenance of Ca^{2+} homeostasis and decreas anterograde axonal transport of mitochondria (De Vos et al., 2012). ATP, adenosine triphosphate; Bcl-2, B-cell lymphoma 2; CytoC, cytocrome c; DRP1, dynamin-related protein; FUS/TLS, fused in sarcoma; GSGG, glutathione disulfide; GSH, glutathione; MPTP, mitochondrial permeability transition pore; OPA1, optical atrophy 1; ROS, reactive oxygen species; SOD1, Cu–Zn Superoxide dismutase; TDP-43, TAR DNA-binding protein 43; TIM, transporter inner membrane; TOM, transporter outer membrane; VAPB, vesicle-associated membrane protein-associated protein B; I, II, III, IV, respiratory chain complexes; $\Delta\psi$, membrane potential.

axon maintenance (Fischer et al., 2011). Further, mutant SOD1s associate to mitochondria, probably to an increased amount compared to the wild type protein, and mostly on the outer membrane and intermembrane space (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). In this process, protein misfolding and aggregation, that is mediated by free Cysteine residues and prompted by mutations and/or by a pro-oxidant environment (Cozzolino et al., 2008; Ferri et al., 2006; Karch and Borchelt, 2010; Karch et al., 2009), play a central role, because it is likely that entrapment in mitochondria is the driving force that eventually leads to mitochondrial accumulation of the protein. This is particularly interesting, since the regulation of the mitochondrial localization of SOD1 is strictly controlled to respond to the physiological needs of mitochondria, that change as a consequence of variations of oxygen concentration, and mutant SOD1 might lose this regulation with significant consequences on mitochondrial function (Kawamata and Manfredi, 2008).

Some specific targets of mitochondria-associated mutSOD1s have been already identified (Israelson et al., 2010; Kawamata et al., 2008; Pasinelli et al., 2004; Pedrini et al., 2010) and some of them were proposed to be relevant in the pathological ALS context. This is the case for VDAC1, a mitochondrial porin located on the outer mitochondrial membrane and is also a key player in mitochondria-mediated apoptosis that was proposed to be required for the association of misfolded mutant SOD1 with mitochondria (Israelson et al., 2010) and thus mediate its toxicity. However, SOD1 remains associated with mitochondria despite genetic deletion of VDAC1 (Li et al., 2010). Since mating mutant SOD1 mice with VDAC1+/− mice accelerates disease onset and decreases survival (Israelson et al., 2010) it is likely that SOD1 and VDAC1 act independently from their association in generating mitochondrial damage.

Mitochondrial mutSOD1s impinge on the overall mitochondrial protein composition and affects the pattern of mitochondrial protein import in spinal cord but not in other non-affected tissues (Li et al., 2010). This suggests that other, yet undiscovered, protein partners might be recruited by misfolded mutSOD1 in mitochondria that may be particularly relevant for motor neuron maintenance. Consequently, experimental approaches aimed at modifying the process of accumulation and aggregation of mutSOD1s in mitochondria may prove crucial to devise new therapeutic approaches for ALS, or at least for familial ALS linked to mutSOD1. We and others were able to provide circumstantial evidence that localization in mitochondria is both necessary and sufficient for mutSOD1s to drive mitochondrial