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Mutant Cu/Zn-Superoxide Dismutase Induced Mitochondrial Dysfunction in Amyotrophic Lateral Sclerosis

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1. Introduction

Mutations in Cu/Zn superoxide dismutase (SOD1) gene are linked to the motor neuron death in familial amyotrophic lateral sclerosis (FALS). More than 100 missense mutations have been described to cause the disease and are distributed throughout the whole 153 amino acid sequence of SOD1 molecule (Valentine et al., 2005; Boillée et al., 2006). Mutant SOD1 molecules can be grouped according to their biochemical characteristics into wild type-like proteins, that bind metal ions and possess enzymatic dismutase activity (e.g. G93A-SOD1 and G37R-SOD1), and mutant molecules with impaired metal binding capacity, which have significantly reduced dismutase activity (e.g. G85R-SOD1) (Valentine et al., 2005). Therefore, the toxicity of mutant SOD1 is not thought to be mediated by a lack of dismutase activity, but rather by gain of one or more detrimental functions.

The exact nature of the toxic gain of function for mutant SOD1 has not been identified yet. Most of the studies demonstrate a link between the disease pathology and increased oxidative stress. Augmented generation of free radicals and reactive oxygen species (ROS) is thought to be a major contributor to the destruction of motor neurons (Beckman et al., 1994; Wiedau-Pazos et al., 1996; Estévez et al., 1999).

The suggested toxic mechanisms include aberrant mutant SOD1 enzymatic activities (Beckman et al., 1993; Wiedau-Pazos et al., 1996) as well as destabilized SOD1 protein misfolding, causing enhanced aggregation of SOD1 or pathological interaction of SOD1 with other proteins (Stathopulos et al., 2003; Liu et al., 2004).

In a number of studies mitochondrial localization of mutant SOD1 has been implicated in ALS pathogenesis (Liu et al., 2004; Vijayvergiya et al., 2005; Bergemalm et al., 2006; Deng et al., 2006; Ferri et al., 2006) and increased recruitment of mutant SOD1 into mitochondria in the spinal cord might be a reason for death of motor neurons in some forms of familial ALS. However, the detailed mechanisms for toxicity of the mitochondria resident mutant SOD1 are not entirely clear yet. Here we review the current state of the art in the studies on mitochondrial toxicity of SOD1 in ALS.

2. Factors controlling SOD1 translocation to mitochondria and SOD1 activity in mitochondrial intermembrane space

Although the majority of SOD1 is present in the cytosol (Okado-Matsumoto & Fridovich, 2001), a fraction of SOD1 is translocated into the mitochondrial intermembrane space (IMS)

(Sturtz et al., 2001; Higgins et al., 2002). Since SOD1 does not contain mitochondrial targeting sequence, the true physiological function of SOD1 in the IMS remains mostly enigmatic.

In mammalian cells the mitochondrial localization of SOD1 is regulated by the folding state of this enzyme, depending on the intracellular distribution of copper chaperone for SOD1 (CCS), which in turn is regulated by oxygen concentration. Redox status of the cysteine residues in human SOD1 is critical for its retention in mitochondria. The cysteine residues form intramolecular disulphide bonds and interact with CCS (Kawamata & Manfredi, 2008). This regulation appears to be impaired for SOD1 mutants, which can lead to misfolding and aggregation of mutant SOD1 and eventually result in SOD1 accumulation inside the mitochondria. In animal models the mitochondrial association of mutant SOD1 is apparent even before the disease onset (Liu et al., 2004), indicating a causative link of mitochondrial SOD1 to the initiation of pathology.

Even though SOD1 has been suggested to be an important part of the mitochondrial superoxide scavenging system, as previously demonstrated in the yeast (Sturtz et al., 2001) and rat (Iñarrea et al., 2005) mitochondrion IMS, SOD1 activity is kept under redox control in this compartment and undergoes activation upon increased hydroperoxide concentration (Iñarrea et al., 2005).

There are 4 cysteines in the human SOD1 molecule, located at 6, 57, 111 and 144 position of the sequence. The intramolecular disulphide bridge between Cys57 and Cys146 is required for the proper tertiary and quaternary structure and enzymatic activity of SOD1 (Arnesano et al., 2004). Diminished copper loading and reduced intramolecular disulphide bound has been thought to be responsible for increased aggregation potential of G93A and D90A mutant SOD1 (Jonsson et al., 2006).

The maturation and activation of SOD1 in the cytosol is controlled by a number of factors and can be divided in several principal steps. Upon post-translational activation, an SOD1 monomer binds a Zn^{2+} ion. Next ,CCS transiently binds to SOD1 monomer and inserts a Cu^{2+} ion in the molecule (Culotta et al., 1997; Casareno et al., 1998). After the dissociation of SOD1 from CCS, oxidative formation of disulphide bounds takes place (Arnesano et al., 2004; Ding & Dokholyan, 2008), which is followed by dimerisation yielding an active SOD1 molecule (Vonk et al., 2010).

Active SOD1 dimers are not capable of entering mitochondria, in contrast to disulphide reduced apo-SOD1. According to the model proposed (Kawamata & Manfredi, 2008; Reddehase et al., 2009), CCS is first imported into mitochondria by interaction with Mia40, an IMS component critical for protein import to mitochondria. The CCS-Mia40 complex is formed through an intermolecular disulphide bound (Fig. 1.). Further disulphide rearrangement generates oxidized CCS, preventing its escape from the IMS. The activation of SOD1 in IMS is thought to be similar to the activation of SOD1 in cytosol, where SOD1 binds to CCS in the presence of Cu^{2+} ions and oxygen generating an active enzyme retained in IMS (Leitch et al., 2009).

Surprisingly, CCS overexpression in G93A-SOD1 mouse, a widely used transgenic mouse model of ALS, produces severe mitochondrial pathology and accelerates disease course (Son et al., 2007). According to the model above, the potentiation of mutant SOD1 toxicity by CCS overexpression can be explained by the CCS-mediated increase in SOD1 mitochondrial import, leading to enhanced SOD1 aggregation.

In contrast to the model of CCS-dependent activation of mitochondrial SOD1, a number of recent studies suggest that SOD1 in the IMS of intact mitochondria is mostly inactive and an

oxidative modification of its critical thiol groups is necessary for the activation (Iñarrea et al., 2005, 2011; Goldsteins et al., 2008). This activation, at least partly, depends on protein disulphide isomerase (PDI) activity (Iñarrea et al., 2005). On the other hand, the toxicity of mutant SOD1 is not correlated with its aggregation potential but with the ability to form active dimeric molecules (Witan et al., 2008). These findings are in concert with a concept that mitochondrial dysfunction and cell damage are paradoxically induced by SOD1-mediated hydroperoxide production in the IMS (Goldsteins et al., 2008).

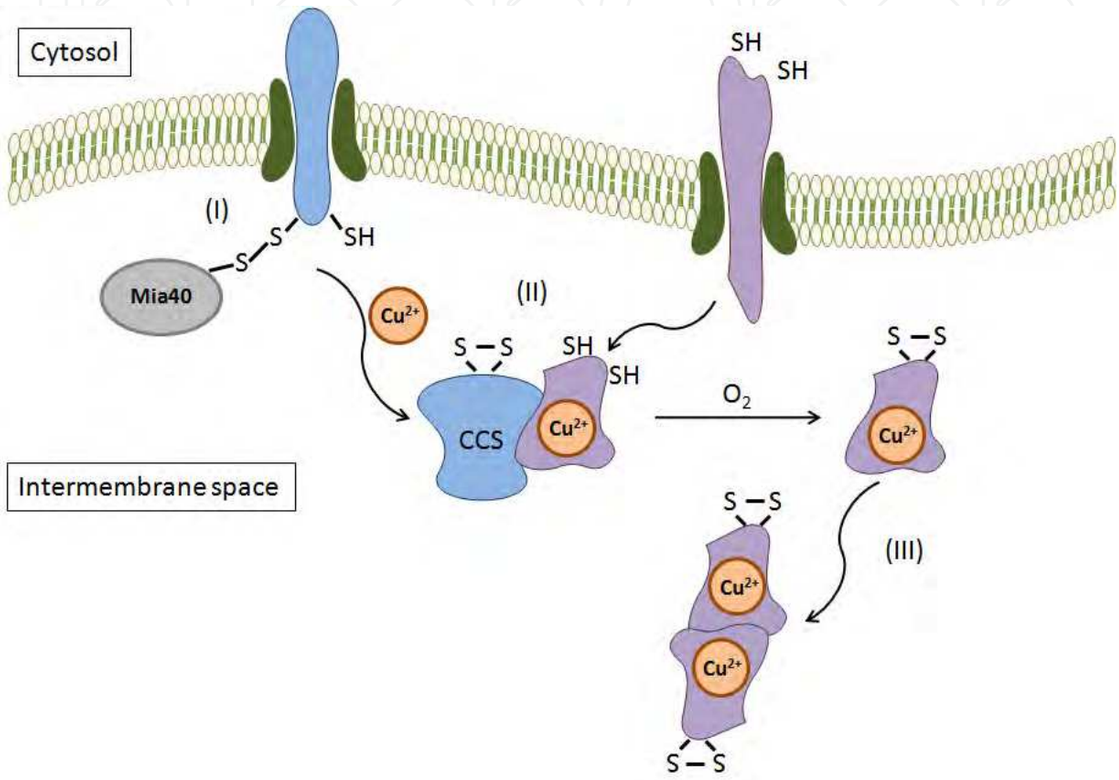

Fig. 1. Import and activation of SOD1 in IMS. CCS is imported into mitochondria through formation of a complex with Mia40 (I). Disulphide-reduced SOD1 monomer enters IMS and acquires copper ion (Cu^{2+}) with a help of CCS (II). Formation of intramolecular disulphide bound and dimerisation of SOD1 creates an active SOD1 molecule retained in IMS (III).

3. Proposed mechanisms for mutant SOD1 toxicity in mitochondria

Mitochondrial abnormalities and degeneration of motor neurons are early signs of ALS disease (Wong et al., 1995; Dal Canto & Gurney, 1997; Kong & Xu, 1998). They also represent pathological hallmarks in mutant SOD1 transgenic animal models for FALS as well as in patients with sporadic ALS (Kong & Xu, 1998; Mattiazzi et al., 2002; Manfredi & Xu, 2005). Mitochondrial toxicity may thus be an important factor in the degeneration of motor neurons. The pathology, demonstrated in sporadic ALS cases includes mitochondrial aggregates, mitochondrion swelling and increased calcium levels in mitochondria (Atsumi, 1981; Siklós et al., 1996). In G93A-SOD1 transgenic mice the disease onset is associated with a remarkable increase of vacuolated mitochondria in motor neurons (Kong & Xu, 1998). It

has been proposed that formation of vacuoles originates from the expansion of mitochondrial IMS and degeneration of mitochondrial matrix (Jaarsma et al., 2001; Bendotti et al., 2001; Higgins et al., 2003; Xu et al., 2004).

Currently, there is no consensus on how mutant SOD1 causes mitochondrial pathology. The proposed mechanisms for mitochondrial toxicity of mutant SOD1 are summarized in Table 1. Among other toxic mechanisms reduced activities of respiratory complexes (Browne et al., 1998), mitochondrial depolarization and impaired calcium homeostasis (Kruman et al., 1999) have been demonstrated in the spinal cord of G93A-SOD1 mice. The observed dysfunctions of mitochondria might be caused by the recruitment of mutant SOD1, which has been shown to be selective to spinal cord mitochondria (Stathopulos et al., 2003; Liu et al., 2004; Pasinelli et al., 2004).

TOXIC MECHANISM	REFERENCES
Aggregate accumulation in mitochondria	(Higgins et al., 2002; Vande Velde et al., 2008)
Aberrant mutant SOD1 enzymatic activities, causing ROS production	(Estévez et al., 1999; Elliott, 2001)
Impaired energy metabolism	(Siciliano et al., 2001; Mattiazzi et al., 2002)
Impaired Ca^{2+} buffering	(Jaiswal & Keller, 2009; Grosskreutz et al., 2010)
Gain in pro-apoptotic function	(Pasinelli et al., 2004)
Interfering with mitochondrial protein import	(Liu et al., 2004)
Increased hydroperoxide production in IMS	(Goldsteins et al., 2008)

Table 1. Proposed mechanisms for mitochondrial toxicity of mutant SOD1

Among the proposed mechanisms, impairment of mitochondrial calcium buffering capacity has been shown in motor neurons of transgenic ALS mice (Damiano et al., 2006). On the other hand, ATP levels have been reported to be diminished in spinal cords of mutant SOD1 mouse model (Mattiazzi et al., 2002). Another view to the mitochondrial toxicity of mutant SOD1 was brought up by Vande Velde et al., who demonstrated that misfolded mutant SOD1 damages mitochondria by its deposition onto the cytoplasmic side of the outer membrane of spinal cord mitochondria (Vande Velde et al., 2008).

Other studies have demonstrated that the increased dismutase activity in rodent ALS models expressing mutant SOD1 paradoxically boosts the production of toxic ROS in the IMS (Goldsteins et al., 2008). It was shown that in a G93A-SOD1 rat model of ALS, the stability and quaternary structure of mutant SOD1 are lost most prominently in the spinal cord already several weeks before the onset of the disease (Ahtoniemi et al., 2008). These results suggest that destabilization of mutant SOD1 is associated with its increased binding to the inner mitochondrial membrane and elevated ROS production in the IMS. (Liu et al., 2004; Kirkinezos et al., 2005; Ahtoniemi et al., 2008).

Importantly, it was also recently demonstrated, that disulphide-reduced apo-SOD1 can rapidly initiate SOD1 fibrillation upon physiological conditions, suggesting that such disulphide-reduced apo-SOD1 may act as a seed for the amyloid like aggregates originating from the destabilized and folding intermediates of mutant SOD1 (Chattopadhyay et al., 2008).

Despite of rather different mechanisms proposed for the toxic properties of mutant SOD1 in mitochondria, most of the recent studies document that mitochondrial dysfunction results in increased ROS production (Beretta et al., 2003). Mitochondria isolated from the neural tissue (brain, spinal cord) have distinct metabolic properties regarding the extent of ROS produced upon oxidation of respiratory substrates (Panov et al., 2011). Especially in G93A-SOD1 transgenic rats, brain and spinal cord mitochondria generate 5–7 fold more ROS than mitochondria of corresponding wild-type tissues. Particularly, the spinal cord mitochondria produce two times more hydroperoxide than brain mitochondria of the same animals (Panov et al., n.d.)

Analysis of mitochondrial morphology in G37R and G85R-SOD1 transgenic mice has revealed that somal mitochondria become shorter and rounder in both dismutase active and inactive mutant SOD1 mouse lines. In contrast, axonal mitochondria in G37R-SOD1 animals shift from elongated tubular mitochondria to punctate mitochondria, while in G85R-SOD1 mice the mitochondria have been reported to show an increase in length (Vande Velde et al., 2011). These changes in mitochondrial shape and distribution were characteristic prior to ALS disease onset and support the notion of early mitochondrial pathology in ALS.

4. SOD1 catalyzes increased hydroperoxide production in IMS

The growing body of evidence provides support to the concept that superoxide dismutation in IMS may cause an increased hydroperoxide production with toxic consequences. Mitochondria are the major intracellular source of superoxide, the primary ROS, where superoxide anion radical is generated by one electron reduction of oxygen.

The two major pathways of superoxide production in mitochondria are autooxidation or complex III catalyzed oxidation of ubisemiquinone (Muller et al., 2004) and complex I catalyzed reduction of oxygen through reversed electron flow in the respiratory chain (Fig. 2.) (Liu et al., 2002). The produced superoxide anion radical has ability to actively react with a number of cellular targets leading to the loss of their proper function. The main detoxifying mechanism for superoxide instead of reverse oxidation of superoxide to oxygen, includes dismutation to hydroperoxide and oxygen.

Besides SOD1, there are other dedicated enzymes catalyzing this dismutation reaction. In mitochondria Mn-superoxide dismutase (SOD2), which is found in the mitochondrial matrix, scavenges superoxide in this compartment. Extracellular superoxide dismutase (SOD3) is secreted into the extracellular space and protects tissues against excess of superoxide (Zelko et al., 2002). In the IMS superoxide is produced presumably by complex III (Fig. 2.) (Muller et al., 2004). Unlike hydroperoxide, which freely diffuses through the membranes, superoxide cannot cross the mitochondrial inner membrane. In the matrix SOD2 converts superoxide to hydroperoxide, which in turn is reduced to water by the matrix glutathione peroxidase (Inoue et al., 2003). Homozygous SOD2 knockout mice are neonatally lethal (Li et al., 1995), whereas deletion of SOD1 gene does not have apparent motor neuron disease phenotype (Maier & Chan, 2002).

In IMS the fate of superoxide is determined by SOD1 and cytochrome c, which is present there in millimolar concentrations (Forman & Azzi, 1997; van Beek-Harmsen & van der Laarse, 2005). Cytochrome c is a heme containing protein, which functions as an electron carrier between complex III and cytochrome oxidase in the respiratory chain. Cytocrome c can also efficiently oxidize superoxide to oxygen. In this respect, cytochrome c can function

as an efficient antioxidant, scavenging superoxide without production of secondary ROS (Fig. 2. reaction II), in contrast to SOD1, which produces hydroperoxide (Fig. 2, reaction III) (Pereverzev et al., 2003). However, cytochrome c has also a potential to catalyze oxidation by hydroperoxide. Upon this reaction, hydroperoxide oxidizes the prosthetic heme in the cytochrome c molecule to oxoferryl heme, forming so-called peroxidase compound I-type intermediate, a highly reactive oxidant that is able to react with a number of intracellular targets including proteins, nucleic acids and lipids, causing cell damage (Fig. 3) (Lawrence et al., 2003). Cytochrome c peroxidase activity is controlled by the coordination state of heme iron, particularly by the sulphur ligand of methionine-80 (Met-80), which can be easily displaced by hydroperoxide (Barr et al., 1996; Qian et al., 2002). The peroxidase activity of cytochrome c may increase by unfolding and post-translational modifications, such as proteolytic cleavage, nitration and oxidation (Diederix et al., 2002; Everse & Coates, 2005; Jang & Han, 2006).

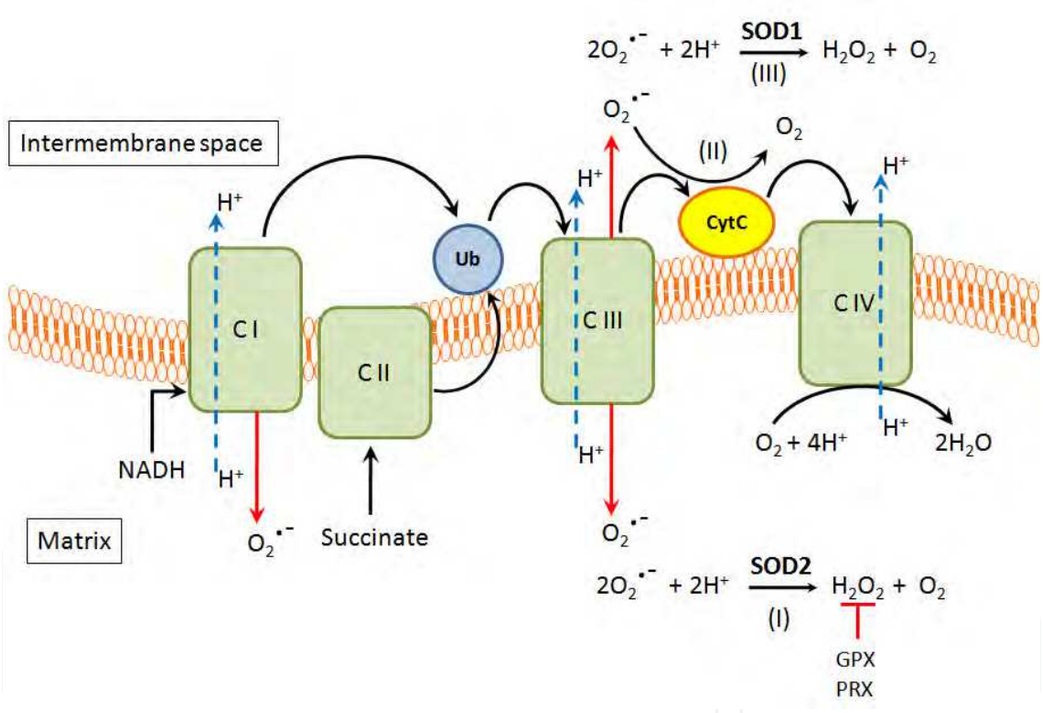

Fig. 2. Mitochondrial production and clearance of superoxide. Upon respiration superoxide is inevitably generated predominantly at respiratory complexes CI and CIII. The superoxide released to the matrix is dismutated by mitochondrial SOD2 (I) and the hydroperoxide produced is cleared by glutathione peroxidase and peroxyredoxins. Most of the superoxide released in IMS is generated at respiratory complex CIII. Oxidized form of cytochrome c, present in the IMS at high concentration can exercise clean clearance of superoxide by its oxidation to oxygen (II). An alternative dismutation catalyzed by SOD1 results in increased hydroperoxide generation in the IMS (III).

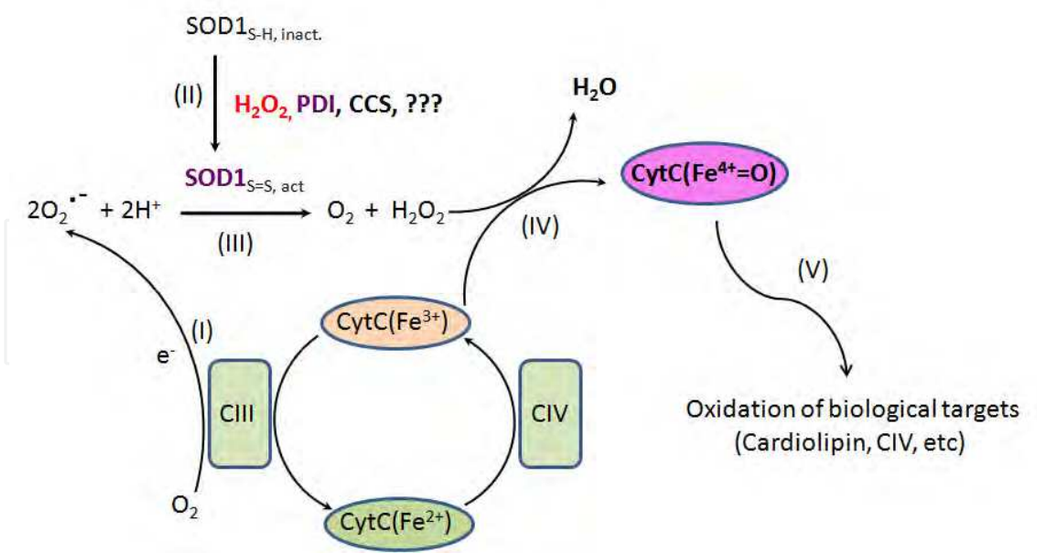

Fig. 3. Deleterious role of superoxide dismutase in the mitochondrial intermembrane space. Superoxide ($O2^{\cdot-}$) is released in IMS by one electron reduction of oxygen at a site in the inner membrane (I). Cu/Zn Superoxide dismutase (SOD1) in IMS is activated by oxidation of cysteine thiols, leading to formation of intramolecular S=S bounds (II). SOD1 produces hydroperoxide (H_2O_2) by dismutating superoxide (III). Hydroperoxide oxydizes cytochrome c (CytC) to oxoferryl-CytC ($CytC(Fe^{4+}=O)$), an exceptionally strong oxidant (IV), able to oxidize a number of vital biological targets (V).

We have recently proposed a model, where upon mitochondrial stress SOD1 may compete with cytochrome c for superoxide in the IMS and generate hydroperoxide, which then could react with cytochrome c and form peroxidase compound I-type intermediate, eventually leading to a deleterious increase in ROS production and cellular injury (Fig. 2) (Goldsteins et al., 2008). According to this model the SOD1-catalyzed superoxide dismutation in the IMS causes paradoxically augmented ROS production.

The data obtained demonstrate that inhibition of electron transfer at the level of complex III leads to SOD1 activation in the IMS, resulting in increased hydroperoxide production and, consequently, cytochrome c-catalyze peroxidation (Goldsteins et al., 2008). This could trigger a vicious circle where oxidative damage to mitochondrial respiratory components leads to further ROS production and peroxidation. Indeed, we have demonstrated that inhibition of mitochondrial respiration at the level of complex III causes SOD1-dependent ROS production and apoptotic death of isolated blood lymphocytes. In contrast, mitochondria isolated from SOD1 knockout mice do not show increased ROS production upon mitochondrial stress. Moreover, accumulation of mutant human G93A-SOD1 in the IMS that is observed in the tg animal models of ALS, leads to elevated SOD1 activity and increased cytochrome c-catalyzed oxidation in the IMS.

Our proposed model provides also an explanation for observations in other neurodegenerative disorders that elevated SOD1 activity worsens the pathology instead of the expected protective effect. For instance, immature mouse brains overexpressing SOD1 show an increased propensity for injury and accumulate more hydroperoxide after hypoxia-ischemia than wt mouse brains (Fullerton et al., 1998). Also, elevation of SOD1 increases acoustic trauma from noise exposure in some models (Endo et al., 2005). Impotantly, mice

deficient in SOD1 have been reported to be resistant to acetaminophen toxicity (Lei et al., 2006). Even though SOD1 as a cytosolic antioxidant protects against mitochondrial dysfunction in a mouse model of transient focal cerebral ischemia (Fujimura et al., 2000), SOD1 deficiency, rather than overexpression, is associated with enhanced recovery and attenuated activation of NF-kappaB after brain trauma in mice (Beni et al., 2006).

This apparent discrepancy concerning the role of SOD1 in cellular injury can be explained by the model introduced, showing that increased SOD1 activity in the IMS paradoxically produces peroxides which are converted to highly toxic ROS. This view is further supported by an observation in mouse model of genetic disorder ataxia-telangiectasia, where elevated levels of SOD1 exacerbate the phenotype of neurodegeneration (Peter et al., 2001). It is also of interest that SOD1 overexpression and high tissue dismutase activity may potentiate atherogenesis in fat-fed atherosclerosis-susceptible mice (Tribble et al., 1997). The evidence about deleterious role of increased SOD1 expression has been most recently complemented by studies demonstrating that overexpression of SOD1 in retina leads to increased hydroperoxide levels and accelerated damage of cone cells (Usui et al., n.d.).

The key component for the SOD1-derived hydroperoxide toxicity in IMS is cytochrome c. Previous studies, including electron paramagnetic resonance (EPR) studies (Barr et al., 1996; Svistunenko, 2005; Belikova et al., 2006; Basova et al., 2007) have demonstrated that the reaction of cytochrome c with hydroperoxide results in formation of oxoferryl cytochrome c (peroxidase compound I-type intermediate) and corresponding protein-derived tyrosyl radical, which is highly reactive and has a potential to oxidize proteins, DNA, and lipids, as well as endogenous antioxidants such as glutathione, NADH, and ascorbate (Lawrence et al., 2003) (Fig. 3). In particular, oxidation of cardiolipin, a phospholipid which is in complex with cytochrome c on the surface of the inner mitochondrial membrane, causes the release of proapoptotic factors from mitochondria (Kagan et al., 2005; Belikova et al., 2006). This leads to a scenario where the hydroperoxide produced by increased SOD1 activity in the IMS, would thus serve as a substrate for cardiolipin-bound cytochrome c and consequently switch on very early proapoptotic processes, inducing consecutive programmed cell death. Additionally, upon increased hydroperoxide levels cytochrome c peroxidase activity may cause NADH oxidation producing a radical, which in turn donates an electron to oxygen augmenting superoxide formation (Velayutham et al., 2011).

The toxicity based on the dismutase activity of mutant SOD1 in the IMS might also be true even for dismutase inactive mutant SOD1 proteins. In human FALS SOD1 mutations are dominantly inherited resulting in the presence of both wild type and mutant SOD1 subunits in each cell. Thus, dismutase activity lacking G85R-SOD1 can form active heterodimers with wt SOD1 molecules. In mice the co-expression of human mutant and wt SOD1 accelerated disease (Jaarsma et al., 2000; Fukada et al., 2001; Deng et al., 2006). Importantly, unaffected A4V-SOD1 mutant mice developed the disease only when mated with human wt SOD1 overexpressing mice (Deng et al., 2006). It was also shown recently that the toxicity of mutant SOD1 dimers is not correlated with their capacity to form protein aggregates but rather with their dismutase activity (Witan et al., 2008).

5. Conclusion

Until now, several pathological mechanisms have been demonstrated how mutant SOD1 induces mitochondrial dysfunction in FALS models. Among them, the emerging evidence indicates that the SOD1-dependant hydroperoxide production in mitochondrial IMS may

fuel the cytochrome c-catalyzed peroxidation and play a key role in oxidation of biological targets in the IMS. Thus, SOD1 activity and factors leading to its increase in this compartment can be regarded as deleterious mechanisms to the mitochondria and the cell. Increased SOD1 activity causing elevated hydroperoxide production in the IMS may be one of general mechanism in neurodegeneration.

At the moment it is not clear how mutations in SOD1 directly affect hydroperoxide production in IMS. One possibility may be the already demonstrated increased mitochondrial import for mutant molecules in neurons of ALS models. Another possible mechanism is linked to less strict dismutase activity control. Altogether, we hypothesize that the mutant SOD1 may gain toxic features because the proper control mechanism for its dismutase activity in mitochondrial IMS may be lost. In conclusion, we suggest that SOD1 activity in the IMS is a relevant therapeutic target for ALS and other neurodegenerative diseases involving mitochondrial pathogenesis.

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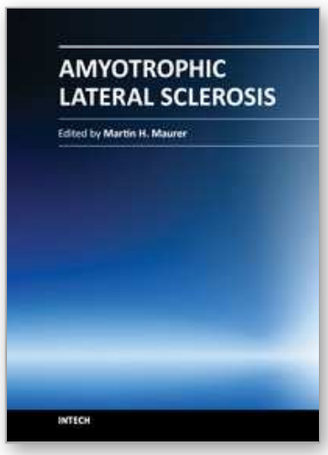

Amyotrophic Lateral Sclerosis

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Though considerable amount of research, both pre-clinical and clinical, has been conducted during recent years, Amyotrophic Lateral Sclerosis (ALS) remains one of the mysterious diseases of the 21st century. Great efforts have been made to develop pathophysiological models and to clarify the underlying pathology, and with novel instruments in genetics and transgenic techniques, the aim for finding a durable cure comes into scope. On the other hand, most pharmacological trials failed to show a benefit for ALS patients. In this book, the reader will find a compilation of state-of-the-art reviews about the etiology, epidemiology, and pathophysiology of ALS, the molecular basis of disease progression and clinical manifestations, the genetics familial ALS, as well as novel diagnostic criteria in the field of electrophysiology. An overview over all relevant pharmacological trials in ALS patients is also included, while the book concludes with a discussion on current advances and future trends in ALS research.

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