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Chapter 1

Pathophysiology of Amyotrophic Lateral Sclerosis

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by death of pyramidal neurons in the motor cortex (upper motor neurons) and motor neurons in the brain stem and central spinal cord (lower motor neurons). This results in muscle weakness, progressive motor disability, and finally death by respiratory failure or an associated infection (Shook and Pioro, 2009). There are two types of ALS familiar (fALS) and sporadic ALS (sALS). They are both clinically undistiguishale one from the other; fALS accounts for 10% of all cases being the rest of the cases sALS (Pasinelli and Brown, 2006). In the last few years, there had been an explosion of genetic studies associating ALS with several genetic mutations in genes codifying for different proteins: Cu/Zn superoxide dismutase, (SOD1), transactive response binding protein 43 (TARDBP), fused in sarcoma (FUS), and valosin containing protein (VCP). Most recently, a genetic defect was identified with an expansion of the noncoding GGGGCC hexanucleotide repeat in the chromosome 9, open reading frame 72 (C9ORF72), associated with ALS with and without frontotemporal dementia (Boeve et al., 2012).

Despite of all these discoveries the etiology of ALS remains elusive. A number of potential pathogenic mechanisms have been associated with ALS including excitotoxicity, mitochondrial dysfunction, apoptosis, glial activation, RNA-processing, growth factor abnormalities, etc. These potential pathogenic processes are reviewed in this chapter.

2. Pathology

ALS is characterized by upper motor neuron (corticospinal motor neurons) and lower motor neuron (bulbospinal motor neurons) degeneration and death as well as reactive gliosis

replacing death neurons (Leigh and Garafolo, 1995). As corticospinal motor neuron degenerate the cells suffer from a retrograde axonal loss with secondary myelin pallor and gliosis. These changes are most severed at the brainstem and upper spinal cord, but are extended throughout the spinal cord (Brownell et al., 1970). ALS motor cortex shows astrocytic gliosis, especially in the deeper layers at the gray matter and underlying the subcortical white matter. Irregular immunoreactivity to GFAP is identified in the motor strip (Kamo, et al. 1987; Ince, 2000). The lysosomal marker CD68 also revealed that most of the glial response at the cortical and spinal tracts corresponds to microglia activation and active macrophages (Cagnin et al., 2001; Sitte et al., 2001). ALS affects spinal motor neurons of the ventral horn and brainstem motor neurons. The autopsy of ALS patients shows loss of motor neurons and atrophic motor neurons with basophilic appearance suggesting a programmed cell mechanism (Martin, 1999). The ventral roots become thin with loss of large myelinated fibers in motor nerves leading to denervation atrophy with evidence of reinnervation in affected muscles. Frontal temporal dementia ALS (FTD-ALS) is a neurodegenerative disorder associated with ALS that presents typical pathological findings of the disease in addition to neuronal loss of the frontal or temporal cortex, hippocampus and amygdale, and spongiform changes of the neocortex with (Leigh PN and Garofolo, 1995). Non-motor findings encountered in ALS pathology are posterior columns demyelination and reduced density of myelinated sensory fibers (Ince, 2007)

2.1. Inclusion bodies

The hallmark finding of lower motor neuron (LMN) pathology in ALS is the presence of intracellular inclusion bodies in neuronal soma and proximal dendrites as well as glia (Barbeito et al., 2004).

2.1.1. Ubiquitylated Inclusions (UBI)

UBI are the most common and specific inclusion in ALS, found at LMN of the spinal cord and brainstem (Matsumoto et al., 1993) and also at the corticospinal tract upper motor neurons (UMN) (Sasaki and Maruyama, 1994). UBI morphological spectrum goes from thread-like ubiquitylated profiles, through skeins of different compactness to more spherical bodies (Ince et al, 1998). The compacted lesions may be eosinophilic, basophilic and "Lewy-like" in appearance. The composition of UBI remains unknown but several proteins were identified in UBI such as ubiquitin (Leigh et al., 1991), peripherin (He and Hays, 2004), Cu/Zn SOD1 (Shibata 1996) and dorfin (Niwa et al., 2002). UBI are present in near 100% of sALS (Ince et al., 2003). However, UBI are found in FTD with ubiquitin positive/tau negative inclusions. In both fALS and sporadic types of ALS-FTD, UBI are found in cortical frontal and temporal lobe neurons.

2.1.1.1. TAR DNA binding Protein 43 (TDP-43)

TDP-43 is a major component of ubiquinated inclusions in sALS, FTD with ubiquitin-positive but tau-negative inclusions (non-tau FTD), FTD-ALS, and non-SOD1 fALS. TDP-43 inclusions are practically not present in mSOD1-related fALS.

2.1.1.2. Fused in Sarcoma protein (FUS)

Recently, mutations in the gene codifying for the fused in sarcoma protein (FUS) have been linked to fALS. Indeed, spinal cord LMNs in fALS and sALS but not in mSOD1-fALS are immunoreactive for FUS inclusions. These inclusions also present immunoreactivity for TDP-43 and ubiquitin (Chaudhuri et al., 1995).

2.1.2. Bunina bodies

Bunina bodies are eosinophilic paracrystalline bodies present in the LMNs of many cases of ALS (Piao et al., 2003). They are immunoreactive for a cysteine protease inhibitor called cystatin C (Okamoto et al., 1993).

2.1.3. Hyaline Conglomerate Inclusions (HCI)

HCI consist of intracellular accumulation of intermediate filament proteins, especially hyperphosphorylated neurofilament subunits and peripherin (Corbo and Hays, 2002), and are found in the motor cortex neurons (Troost et al., 1992). HCI are much less frequently encountered in spinal motor neurons than UBI and they are mainly associated with some types of mSOD1 fALS. They form a larger conglomeration than UBI and are positive for silver staining, contrary of UBI. (Ince PG and Wharton S, 2007).

3. Oxidative stress

Mutations in the gene of copper/zinc superoxide dismutase type 1 (SOD1) are the most common cause of fALS (Rothstein, 2009; Boillee and Cleveland, 2008; Robberecht and Phillips, 2013). Recent reports indicate that SOD1 mutations may also be the cause of between 0.7 - 4% cases of sporadic ALS (sALS) (Robberecht and Phillips, 2013). SOD1 is primarily an antioxidant metalloenzyme that catalyzes the conversion of superoxide radical ($O_2^{\cdot-}$) to oxygen (O_2) and hydrogen peroxide (H_2O_2). However, SOD1-linked fALS is most likely not caused by loss of the normal SOD1 activity, but rather by a gain of a toxic function. One of the hypotheses for mutant SOD-linked fALS toxicity proposes that an aberrant SOD1 chemistry is responsible for the toxic gain-of-function, which allows small molecules such us peroxynitrite or hydrogen peroxide to produce damaging free radicals. Other hypotheses for mutant SOD1 neurotoxicity include inhibition of the proteasome activity, mitochondrial damage, and formation of intracellular aggregates. SOD1 aggregation is an early event in ALS and could mediate motor neuron degeneration via sequestration of cellular components, decreasing chaperone activity and the ubiquitin proteasome pathway. Also, SOD1 mutations seem to disrupt RNA processing in the cells.

Defining the role of oxidative stress, and particularly nitrative stress in neurodegeneration has been extremely difficult because of the multiplicity of potential targets that can be damaged by oxidation and nitration. Certain proteins are particularly susceptible to tyrosine nitration by the oxidant peroxynitrite ($ONOO^-$). Tyrosine nitration is a well-established, early biomarker

in ALS and it has been proposed that in fALS mutant SOD1 produces motor neuron death by allowing peroxynitrite formation and catalyzing tyrosine nitration, which in turn inhibits trophic signals (Estevez et al., 1999; Beckman et al., 1993; Crow et al., 1997; Ischiropoulos et al., 1992; Franco and Estevez, 2011). Motor neurons are highly dependent on a continuous supply of trophic factors to survive both *in vivo* and *in vitro*. Deprivation of trophic support *in vivo* by ventral root avulsion in adult animals and axotomy in newborns, but not in adults, triggers apoptosis (Li et al, 1994; Oppenheim, 1997; Gould and Oppenheim, 2011). Induction of apoptosis in these conditions is preceded by induction of neuronal nitric oxide synthase (nNOS) and nitric oxide production. Motor neuron death induced by trophic factor deprivation requires protein synthesis and caspase activation both *in vivo* and *in vitro* (Milligan et al., 1994; Li et al, 1998; Yaginuma et al, 2001). Cultured motor neurons deprived of trophic factors induce nNOS expression, production of nitric oxide and peroxynitrite formation that is followed by tyrosine nitration, which precedes motor neuron death (Estevez et al., 1998). Inhibition of nitric oxide production and peroxynitrite formation prevents rather than delays motor neuron death, suggesting that peroxynitrite is acting at decision-making points in the apoptotic cascade. Deprivation of trophic factors activates the Fas pathway in motor neurons, and inhibition of the Fas pathway prevents motor neuron death. Fas activation in motor neurons triggers two parallel pathways: the classical extrinsic pathway recruiting FADD and Caspase 8; and a seemingly motor neuron specific pathway, that activates DAXX/ASK1/p38 and the induction of neuronal NOS, increasing production of nitric oxide, peroxynitrite formation and tyrosine nitration (Raoul et al, 2002).

4. Excitotoxicity

4.1. Glutamate

A dominant hypothesis of ALS pathogenesis is glutamate excitotoxicity. Glutamate is the major excitatory neurotransmitter found in mammalian central nervous system (CNS) however, in high concentrations is toxic to motor neurons. Some of the evidence supporting glutamate excitotoxicity was based on the observation that exposure of neuronal cell cultures to excess glutamate leads to cell death (Choi et al 1988). A similar observation was made in anterior horn cells in tissue cultures of rat spinal cord where incubation with high concentrations of glutamate is associated with cell loss (Silani et al 2000). In addition, defects in glutamate transport leading to elevated glutamate levels have been reported in mSOD1 mice and significant number of patients with sALS (Dunlop et al., Lin et al., Rothstein et al.,). Elevated glutamate levels were found in serum and spinal fluid of patients with sALS (Al-Chalabi, et al 2000; Rothstein et al., 1990; Shaw, et al, 1995). Another study showed that 40% of about 400 patients with sALS have an elevation in glutamate levels that correlates with the severity of the disease (Spreux-Varoquax et al., 2002)

The mechanism of glutamate neurotoxicity remains elusive. Excessive glutamate levels lead to activation of glutamate ionotropic AMPA receptors in neurons and glial cells. AMPA receptor activation triggers mitochondrial changes such as reduction in ATP synthesis,

decreased cellular oxygen consumption, oxydative phosphorylation uncoupling, and increase in mitochondrial reactive oxygen species (ROS) production, causing a loss in the mitochondrial calcium buffer properties and apotosis (Heath and Shaw 2002) (Fig. 1). Rapid clearance of glutamate at the synapsis cleft is an essential step in the prevention of motor neuron excitotoxicity. This step accomplished by the astrocyte glutamate transporter excitatory amino acid-2 (EAAT2) (Rothstein et,al 1996). In transgenic mice, depletion of EAAT2 has been implicated with neuronal death (Rothstein et,al 1996). Abnormalities in EAAT2 expression were identified in two rodent models of fALS. In the $SOD1^{G85R}$ transgenic mice a ~ 50% decrease in EAAT2 expression was observed in the spinal cord at the end of the disease (Bruijin et al., 1997), while in the spinal cord ventral horn of transgenic $SOD1^{G93A}$ rats EAAT2 expression was decreased before the symptomatic stage of the disease and was almost undetectable at the end of the disease (Howland et al., 2002). Reduction in the expression of EAAT2 was found in motor neuron disease (Fray et al 1998) and decreased glutamate transport was identified in motor cortex and spinal cord in ALS (Rothstein et al., 1992) (Fig. 1).

4.2. Glutamate receptor

An alteration in the expression of the glutamate receptor was found in motor neurons expressing mutant SOD1, suggesting that excitotoxicity is not only induced by increased glutamate levels but also by alterations in the glutamate signaling pathway (Spalloni et al., 2004). In oocytes co-expressing A4V or I113T-SOD1 with EAAT2, the mutants but not the wild type SOD1 selectively inactivated the glial glutamate transporter in the presence of hydrogen peroxide. This suggests that EAAT2 may be a target for mutant SOD1 toxicity (Trotti et al., 1999). On the other hand, overexpression of EAAT2 in mutant SOD1 expressing mice delayed the onset of motor neuron disease and decreased caspase 3 activation, the final step of the apoptotic pathway (Guo et al 2003). In motor cortex and spinal cord extracts from ALS patients, 25% of the patients showed almost complete loss of EAAT2 protein, and 80% of the patients showed some sort of protein abnormality (Rothstein et al., 1995) (Fig.1).

Glutamate receptor dysfunction is other possible route of excitotoxicity. Glutamate toxicity in motor neurons is primarily mediated via alpha-amino-3-hydroxy-5-methyl-4 isoxazole propionic acid (AMPA) receptors (Van Den Bosch et al., 2000). In patients with ALS, a deficiency in the AMPA receptor mRNA expression was found in spinal motor neurons (Kawahara, et al., 2004). This defect results in an increase in calcium influx through the receptor leading to cell damaged. The increased entry in calcium in addition to the reduction in the calcium buffer capacity due to abnormal mitochondria result in an increase in free intracellular calcium levels, leading to motor neuron death (Bogaert et al., 2010) (Fig.1). Additionally, the expression of the glutamate receptor subunits is reduced in ALS motor neurons (Williams et al 1997). Another pathway leading to excitotoxicity is via deficiency in glutamate dehydrogenase activity (Pioro et al., 1999).

The modest protection conferred by the antigluaminergic drug riluzole in ALS patients as well as in mutant SOD1 mice seems to support the effect of glutamate toxicity in the pathogenesis of ALS (Lacomblez et al., 1996; Gurney et al., 1996). However, whether riluzole protects by a mechanism related to its antiglutaminergic properties needs to be established.

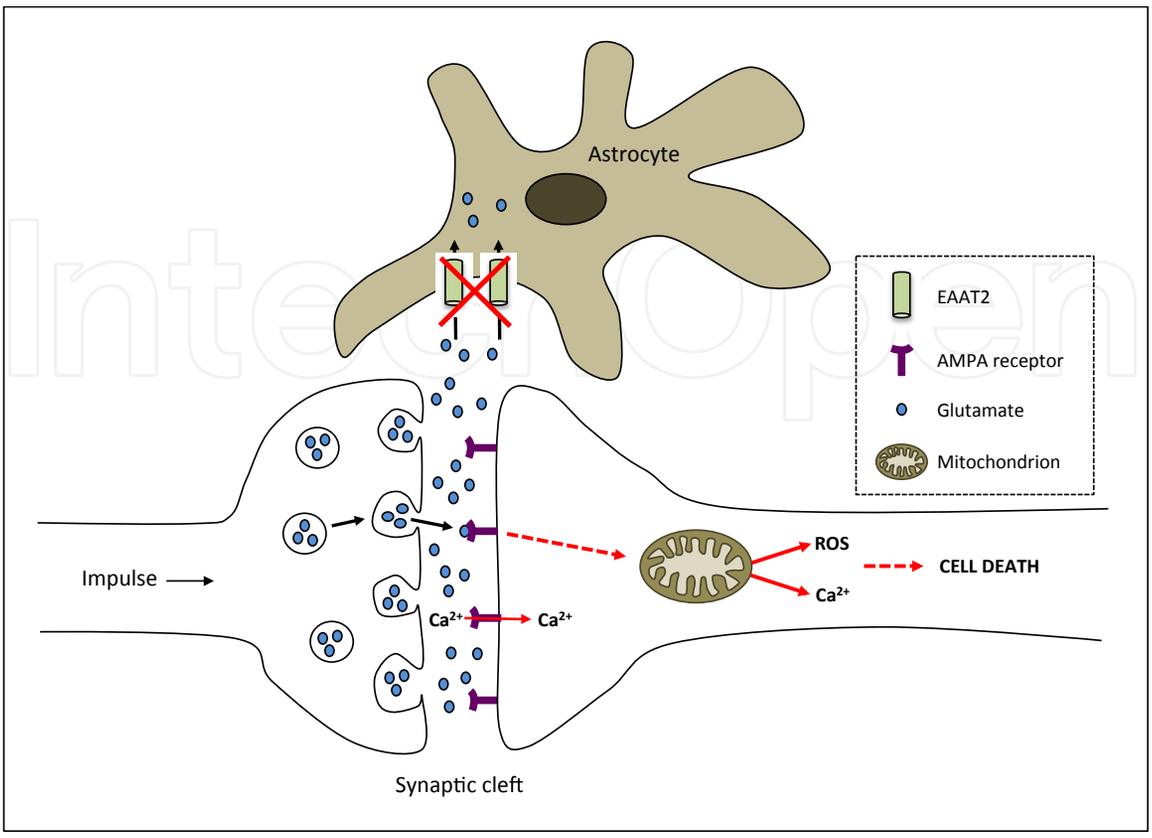

Figure 1. Induction of motor neuron death by glutamate excitotoxicity. Red arrows/lines indicate the pathways that are affected or induced in ALS.

5. Mitochondrial abnormalities

The mitochondrion is a vital organelle with multiple functions within cells. Mitochondria are the main source of ATP, maintain calcium homeostasis and participate in calcium signaling, and play a key role in the intrinsic apoptotic pathway. Mitochondrial malfunction turns motor neuron more vulnerable to damage, especially in aging and stress neurons. Mitochondrial malfunction is an important hypothesis in ALS pathogenesis (Bruijn et al., 2004; Manfredi et al., 2005).

5.1. Mitochondrial morphology

Indeed, mitochondria morphological and ultrastructural changes as well as bioenergetic malfunction have been reported in ALS. SOD1 is localized mainly in the cytoplasm, but has been found also in the mitochondria and other organelles (Okado et al., 2001; Sturtz et al., 2001). Mutant SOD1 protein is present in the mitochondrial intermembrane space, matrix and outer membrane of mitochondria (Higgins, et al, 2002; Vijayvergiya et al., 2005; Vande Velde et al., 2008; Kawamata et al., 2008). This abnormal SOD1 protein may fail to fold properly

resulting in mitochondrial protein retention and mitochondrial dysfunction with damaged of the mitochondrial membrane and loss of mitochondrial membrane potential and swelling (Wong et al., 1995; Kong et al., 1998). Severe mitochondrial morphological changes were found in NSC34 cells overexpressing mutant SOD1 (Raimondi et al., 2006; Menzies et al., 2002). In addition, mitochondrial swelling and vacuolization in motor neuron axons and dendrites were reported in mSOD1 mice even before disease onset (Wong et al., 1995; Kong et al., 1998; Borthwick et al., 1999). The presence of abnormal mitochondrial clusters was also described in mutant SOD1 rat motor axons (Sotelo-Silveira et al., 2009) as well as in lumbar spinal cord motor neurons and proximal axons of sALS patients (Sasaki et al., 1996; Hirano et al., 1984).

5.2. Electron transport chain

Abnormal respiratory complex activities, disrupted redox homeostasis and decreased ATP production were described in ALS (Borthwick et al., 1999; Jung et al., 2002; Bowling et al., 1993; Ferri et al., 2006). Biochemical studies showed several abnormalities in mitochondrial electron transport chain. The enzymatic activity of the electron transport chain complexes I, II, IV was reduced in mSOD1 mice and cell cultures from patients with fALS (Jung et al., 2002; Mattiazzi et al., 2002). The interaction between cytochrome c and the inner mitochondrial membrane in addition to the activity of complex IV were reduced in the $SOD1^{G93A}$ transgenic mice (Kirkinezos et al., 2005). Decreased oxygen consumption, lack of ADP-dependent respiratory control, and decreased membrane potential were also reported in mutant SOD1 rat spinal astrocytes (Cassina et al., 2008) (Fig. 2).

5.3. Calcium homeostasis

Mitochondria play an important role in the intracellular calcium homeostasis as a calcium buffer, accumulating or releasing calcium depending on the cytosolic levels. Abnormalities in mitochondrial calcium homeostasis were reported in ALS patients and in mutant SOD1 animals (Kruman et al., 1999; Carri et al., 1997; Reiner et al, 1995; Jaiswal et al., 2009). The release of calcium from the mitochondria leads to excessive intracellular calcium levels. This abnormal calcium homeostasis induces motor neuron death through several mechanisms including: 1) toxic generation of reactive oxygen species (ROS), as reported in $SOD1^{G93A}$ transgenic mice (Kruman et al., 1999); 2) release of cytochrome c from the mitochondria (Martin et al., 2009); 3) glutamate excitotoxicity (Nicholls et al., 2003), and others. All these mechanisms may have a special role in motor neurons because these cells contain less mitochondrial density per volume compared to non-neuronal cells, thus making neurons more deficient in mitochondrial calcium buffering properties (Grosskreutz et al., 2007) (Fig. 2). In addition, ALS patients show a deficiency in calcium binding proteins calbidin and paralbumin in cortical motor and spinal motor neurons. These two proteins regulate intracellular calcium levels and their deficiency may result in neuronal loss. On the contrary, oculomotor neurons or neuron from the Onuff's nuclei contains normal levels of calbidin and paralbumin levels and they are preserved despite ALS progression (Alexianu, et al. 1994; Celio, 1990; Ince et al., 1993, Palecek et al., 1999).

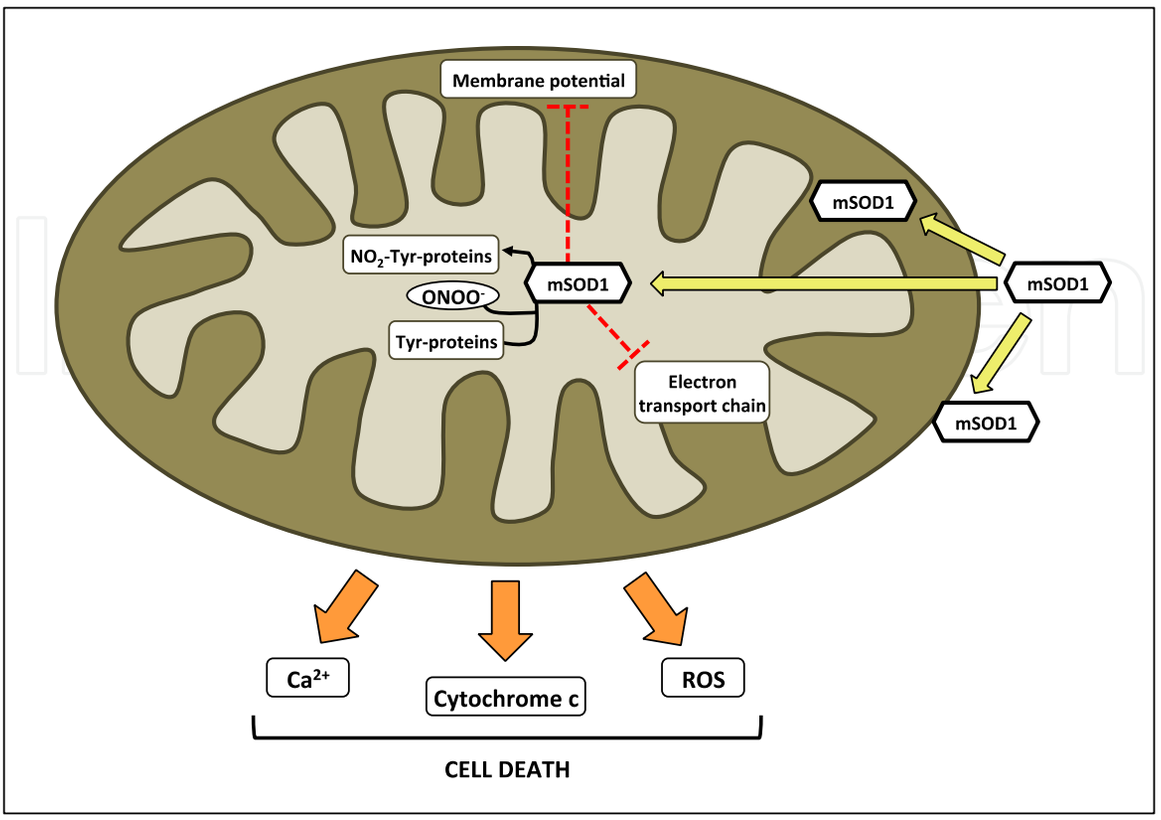

Figure 2. Mitochondrial abnormalities associated with mutant SOD1 (mSOD1). Mutant SOD1 translocates to mitochondrial intermembrane space and matrix, and is associated with the mitochondrial outer membrane. The expression of mutant SOD1 is linked to decrease of mitochondrial membrane potential and electron transport chain activity. The release of calcium and cytochrome c to the cytosol, and the production of ROS lead to cell death in ALS.

6. Axonal transport abnormalities

Transport of proteins, vesicles, and organelles between cell body and terminal axons is a vital process in neuronal development, function and survival. Cytoskeletal proteins such as neurofilament (NFs) confer structure and shape to motor neurons, and are involved in axonal anterograde and retrograde transport between soma and motor axons. NFs are intermediate filaments made from the assembly of light, medium, and heavy subunits (Maragakis and Galvez-Jimenez, 2012). Disorganization of NFs affects axonal transport resulting in axonal strangulation and accumulation of axonal cargo (Collard et al., 1995). A hallmark of ALS pathology is the abnormal accumulation of NFs in the neuronal cell bodies and proximal axons. Animal models and patients with ALS show that axonal transport is a critical component in ALS pathogenesis (Morrison et al., 1998; Lin et al., 2006). Transgenic models of fALS and sALS are associated with mutations of the heavy NF subunits (Figlewicz et al., 1994; Al-Chalabi et al., 1999). In addition, reduction in light subunit mRNA levels was found in motor neurons from the spinal cord of patients with ALS (Wong et al., 2000). Abnormal axonal transport, vacuolization and degeneration of axons and motor neurons have been reported in transgenic

mice overexpressing or with reduced expression of NF subunits (Collard et al., 1995; Cote et al., 1993). In neurons, mitochondria are frequently found in axon terminals due to the high demand of ATP and calcium handling at the synapses (Shepherd et al., 1998; Rowland et al., 2000). Mitochondria are transported in both anterograde and retrograde directions via kinesin and dynein motor complexes (Nangaku et al., 1994; Zhang, et al 2004; Varadi et al., 2004). The disruption of the mitochondrial axonal transport has been implicated in neurodegenerative diseases including ALS (Hollenbeck et al., 2005; De Vos et al., 2007; Magrane et al. 2009). Mitochondria display saltatory movement along microtubules. In $SOD1^{G93A}$ transgenic mice and cortical neurons transfected with G93A-SOD1, mitochondrial transport was selectively reduced in the anterograde direction (De Vos et al., 2007). In addition, in NSC34 cells overexpressing mutant SOD1 mitochondrial transport was altered in both anterograde and retrograde directions (Magrane et al., 2009). Abnormalities in axonal transport cause abnormal renewal of mitochondria and autophagosomes at distal motor axons resulting in mitochondrial accumulation, deficit in energy production, accumulation of ROS, and released of pro-apoptotic agents leading to neuronal death. Slow axonal transport impairment has been described as one of the earliest pathological events in mSOD1 mice (Williamson et al., 1999; Zhang et al. 1997). Fast axonal transport is mediated by kinesin while dynein motor complexes mediate the transport of membrane-bound organelles necessary for axonal and synaptic functions. In patients and transgenic rodent models of ALS there are impairments in the kinesin-mediated anterograde transport and dynein-mediated retrograde axonal transport (Williamson et al., 1999; Breuer et al 1987; Breuer et al., 1988; Collard et al., 1995; Sasaki et al., 1996; Ligon et al., 2005; Parkhouse et al., 2008). Disruption of kinesin heavy chain KIF5B causes perinuclear clustering of mitochondria in mice neurons, indicating that KIF5B is essential for mitochondrial dispersion (Tanaka et al., 1998). Abnormalities in the transport of other proteins such as dynactin, myosin and actine were also identified in transgenic mutant SOD1 models (LaMonte et al., 2002). Dynactin mutations have been associated with autosomal familiar motor neuron disease (Puls et al 2003; Puls et al 2005). Peripherin, another intermediate transport filament was found in neuronal inclusions of sALS (Corbo et al., 1992). Overexpression of peripherin in transgenic mice is associated with axonal degeneration. Inflammatory cytokines increased peripherin levels, suggesting an association between inflammation and axonal transport disorders (Sterneck, et al 1996).

7. Growth factors

Several growth factors (GFs) has been investigated and potentially implicated in the pathogensis of ALS. One of the most studied GFs is the vascular endothelial growth factor (VEGF), a protein involved in vasculogenesis and angiogenesis, and in restoration of oxygen supply upon limited blood circulation. Animal data suggest that VEGF may be neuroprotector. Overexpression of VEGF delayed onset and progression motor neuron disease, as shown in a double transgenic mice generated by crossing mice expressing human mutant SOD1 with mice overexpressing neuronal VEGF (mSOD1/VEGF). The mSOD1/VEGF transgenic mice showed a delayed in motor neuron loss, motor impairment, and a prolonged survival compared with

mutant SOD1 transgenic mice (Wang et al., 2007). Intracerebroventricular administration of VEGF in a $SOD1^{G93A}$ rat model of ALS delayed motor neuron degeneration and onset of paralysis, improved motor performance, preserved neuromuscular junction, and extended survival (Storkebaum et al., 2005). This study also showed that in $SOD1^{G93A}$ mice, neurons expressing a transgenic VEGF receptor prolonged mice survival. Also supporting the VEGF neuroprotective role, a single injection of a VEGF-expressing lentiviral vector into several muscles of $SOD1^{G93A}$ mice delayed the onset as well as the progression of the disease even at onset of paralysis (Azzouz et al., 2004). Interestingly, mouse models in which the hypoxia-response element in the VEGF gene was deleted showed a decrease in VEGF expression in normoxia and under hypoxic conditions. This model resulted in a progressive motor neuron degeneration disease that resembles ALS (Oosthuyse, et al., 2001). A meta-analysis of over 900 individuals from Sweden and over 1,000 individuals from Belgium and England with a specific haplotype for VEGF associated with reduced circulating VEGF and VEGF gene transciption showed a two-fold increase in the risk of developing ALS for these individuals (Lambrechts et al., 2003). In another study, $SOD1^{G93A}$ mice crossed with VEGF haplotype mice showed a much more severe motor neuron degeneration. VEGF probably has neuronal direct and indirect neuroprotective effects preventing ischemic changes while regulating vascular perfusion.

Additionally, VEGF-B, a homolog of VEGF with minimal angiogenetic activity, was shown to be protective for cultured primary motor neurons. In addition, transgenic mice with deletion of the VEGF-B gene were implicated in an ALS-like pathogenesis, as shown crossing a VEGF-B knockout mouse with transgenic mice expressing human mutant SOD1 (mSOD1/VEGF-$B^{-/-}$) (Poesen et al., 2008). mSOD1/VEGF-$B^{-/-}$ mice showed an earlier death and more severe motor neuron degeneration compared with mutant SOD1 transgenic mice. Intracerebroventricular administration of VEGF-B in a $SOD1^{G93A}$ rat model of ALS prolonged the survival of mutant SOD-expressing rats, suggesting that VEGF is neuroprotective by a mechanism independent of angiogenesis (Poesen et al., 2008).

Other beneficial growth factors are innsuline growth factor-1, glial cell line –derived neurotrophic factor, and brain derived neurotrophic factor.

8. RNA metabolism disorders

Ubiquinated intracytoplamsmatic inclusions containing trans-activation response DNA-binding protein of 43 KDa (TDP-43), encoded by the TARDBP gene in chromosome-1, had been identified in motor neurons of patients with sALS and frontal lobar degeneration (FTLD) linked to TDP-43 pathology (FTLD-TDP) (Neumann et al., 2006). TDP-43 positive inclusions were also identified in patients with non-SOD1 fALS. Gene mutations of the TDP-43 gene probably accounts for 5% of patients with fALS. All the cases of sALS and SOD1 negative fALS have neural and glial inclusions immunoreactive to both ubiquitin and TDP-43 whereas positive SOD1 mutations in fALS were absent of TDP-43 immunoreactivity. (MacKenzie et al., 2007; Tran et al., 2007). TDP-43 inclusions were also identified in patients with Guamanian

parkinsonism-dementia complex, and familial British dementia (Sreedharan et al., 2008; Kabashi et al., 2008; Van Deerlin et al., 2008; Yokoseki et al., 2008; Rutherford et al., 2008; Del Bo et al., 2009; Hasegawa et al., 2007; Schwab et al., 2009). TDP-43 is a nuclear protein expressed in almost all tissues that binds to mRNA and DNA and regulates mRNA processing processes such as splicing, translation, and gene transcription. TDP-43 structure consists of two RNA recognition motifs (RRMs) that bind to nucleic acids, and a glycine rich domain containing the majority of ALS associated mutations (Cohen et al., 2012; Buratti et al., 2001). Genetic mutation of another RNA processing protein, fused in sarcoma /translated in liposarcoma (FUS/TLS), has been also associated with ALS (Kwiatkowski et al., 2009; Vance et al., 2009). The FUS/TLS has a similar structure to TDP-43 with RRM and glycin rich domains. FUS/TLS, also a nuclear protein, accumulates in intracytoplasmatic tau- and TDP-43 negative inclusions in patients with fALS, sALS, and frontal lobar degeneration FTLD-FUS (Mackenzie et al., 2010). TDP-43 and FUS/TLS stabilized mRNA encoding histone deacetylase 6 (HDAC6) involved in clearance of misfolded protein aggregates (Kim et.al, 2010, Fiesel, et al., 2010; Lee et al., 2010; Kawaguchi et al., 2003). TDP-43 binds to a wide range of RNA targets and promotes the synthesis of several proteins implicated in the neuronal development and integrity (Tollervey et al., 2011). TDP-43 expression is carefully controlled by a tightly autoregulated mechanism (Winton et al., 2008). Thus, TDP-43 abnormalities in RNA binding and autoregulation, and FUS/TLS may have a essential role in neuronal integrity. TDP-43 also has a protective effect on mitochondrial function; abnormal expression of mitochondrial fission/fusion proteins in transgenic mice expressing human wild-type TDP-43 transgene driven by mouse prion promoter had been reported (Xu et al., 2010). In cultured cells, exposure to stress caused TDP-43 to be relocated into stress granules (SGs). This abnormal localization of TDP-43 could start a pathological TDP-43 aggregation or TDP-43 interaction with other SGs-proteins. A similar process may occur with FUS/TLS protein (Bosco et al., 2010; Dormann et al., 2010). The formation of SGs may lead to pathological inclusion aggregations resulting in neuronal and glial cell damage. Hyperphosphorilated TDP-43 aggregates were identified in ALS spinal cord and FTLP-TDP brain tissue. TDP-43 glycin-rich domain, where most of the mutations had been identified, seems to be required for TDP-43 association with SGs. Expression of insoluble aggregates of TDP-43 terminal fragment was implicated in the generation of SGs (Liu-Yesucevitz et al., 2010). In addition, TDP-43 interacts with cytoplasmatic Ataxin-2 protein resulting in TDP-43 accumulation in misfolded aggregates. Mutant polyglutamine expansions within ataxin-2 enhanced the binding to TDP-43 facilitating the formation of aggregates in ALS patients (Elden,AC et al., 2010). The formation of these aggregates seems to be implicated in neuronal death, but the mechanism remains elusive.

9. Non-cell autonomous mechanisms

Evidence is accumulating indicating that motor neuron degeneration in ALS is not only restricted to neuronal autonomous cell death but it is rather a more complex process involving inflammatory neurotoxicity from non-neuronal glial cells such as astrocytes and microglia (Phani et al., 2012). Support for non-autonomous evidence comes from several studies in

transgenic mutant SOD1 mice. The expression of mutant SOD1 restricted to motor neurons *in vivo* was not enough or caused a mild neurodegeneration (Jaarsma et. al.; 2008). Indeed, when mutant SOD1 expression was reduced in microglia and macrophages there was a reduction in motor neuron degeneration (Boillee 2006, Wang 2009). In addition, mutant SOD1 expression in astrocytes is required to cause neurodegeneration by release of toxic factors (Gong et. al., 2000; Nagai et al. 2007). Co-cultures of healthy motor neurons with astrocytes expressing mutant SOD1 resulted in more than 50% motor neuron death (Marchetto et al, 2008), while astrocytes obtained from postmortem tissue from patients with fALS and sALS were both toxic to motor neurons (Haidet-Phillips et al., 2011). In agreement, mutant SOD1 knockdown in astrocytes attenuated toxicity towards motor neurons, suggesting that the mutant enzyme plays a role in both fALS and sALS (Phillips et al., 2011). $SOD1^{G93A}$ glial-restricted precursor cells transpanted into the cervical spinal cord of wild type rats survived and differentiated efficiently into astrocytes. These graft-derived $SOD1^{G93A}$ astrocytes induced host ubiquitination and death of motor neurons, reactive astrocytosis, and reduction of the glial glutamate transporter GLT-1 expression that was associated with animal limb weakness and respiratory dysfunction (Papadeas et al., 2011). The $SOD1^{G93A}$ astrocyte-induced motor neuron death may be madiated by host microglial activation (Papadeas et al., 2011).

Abnormalities in the immune system have also been observed in ALS patients. Blood samples of ALS patients have increased levels of $CD4^+$ cells and reduced levels of $CD8^+$ T lymphocytes. However, early in the disease when motor features are still mild there is a reduction in $CD4^+$/$CD25^+$ T-regulatory cells (T-reg) and $CD14^+$ monocytes. These observations suggest that the reduction in circulating T-reg cells could be due to the relocation of the cells into the central nervous system. Upon relocation, the T-reg cells would activate the innate immune cells like microglia, leading to the release of anti-inflammatory cytokines such as interleukin-10 and transforming growth factor-β to protect the affected area (Kipnis et al., 2004 and Mantonavi, et al., 2009). Indeed, immunostaining for the astrocytic marker glial fibrillary acid protein (GFAP) showed a significantly increased presence of astrocytes in the precentral gyrus of patients with both fALS and sALS. In addition, staining for activated microglia and macrophages markers such as leukocyte common antigen (LCA), lymphocytes function associate molecule (LFA-1), complementary receptors CR3 (CD11b), and CR4 (CD11c) was also increased in motor cortex, brainstem, and corticospinal tract (Kawamata, et al., 1992; Papidimitriou et al., 2010). Samples from brain and spinal cord from animal models and patient with ALS also showed a significant increase in activated or reactive astrocytes, an indication of neuroinflammation (Sta et al., 2011).

Astrocytes and microglia play an essential role in immune surveillance and response in the central nervous system. Reactive astrocytes recruited to the injured area reestablish the blood-brain-barrier (BBB), release neurotrophins and growth factors (IGF-1), clear debri, and isolate the injured region through the formation of a glial scar (Papadimitriou et al 2010; Dong and Benviste 2001). Microglia are also activated in the presence of antigens exposed during neurodegeneration leading to the phagocytosis of cellular debri and the secretion of several neurotrophic factors, neurotrophins, and cytokines. However, a poor regulation of these factors could be harmful to motor neurons. Microglia seems to protect motor neurons from

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neurodegeneration, but is activated in the first steps of neurodegeneration. An increase in the immunostaining for GFAP and CD11 suggests the presence of reactive astrocytes and microglia in SOD1 transgenic mice (Fischer et. al, 2004). Increase in NGF, a sign of reactive atrocytes, leads to aptoptosis in ALS through a pathway involving activation of p75 (Pehar et al., 2004). Additionally, in ALS animal models mutant SOD1-expressing astrocytes are neurotoxic to motor neurons, and reducing mutant SOD1 expression decreases motor neuron degeneration and increases animal life span (Lepore at al., 2008, Barbeito et al., 2010). The release of pro-inflammatory cytokines, oxidative stressors such as prostanglandins, leukotrienes, and reactive nitrogen species (RNS) is toxic to motor neurons (Henkel, et al., 2009). In *in vitro* studies, normal motor neurons die through a pro-apoptotic Bax pathway when co-cultured with astrocytes expressing mutant SOD1 (Nagai at al., 2007). In *in vivo* studies, microglia releases pro-inflammatory cytokines such us TNF-α and IL-1β as well as ROS (Henkel 2009) whereas in ALS patients, there is an increase of pro-inflammatory cytokines and prostranglandin E2 (Papadimitou, 2010). Media obtained from activated microglia causes motor neuron death by activation of TNF-α and NMDA receptors (Moisee and Strong 2006). In mouse model of ALS, a reduction in the expression of mutant SOD1 by microglia does not change age of symptoms onset, but slowed down disease progression (Boillee et al. 2006b). Motor neurons expressing mutant SOD1 are more susceptible to Fas ligand and NO-triggered cell death (Raoul et al., 2002), suggesting that in the context of ALS progression, motor neurons expressing mutant SOD1 are more vulnerable to external stimuli such as ROS, RNS and toxic factors release by surrounding cells.

10. Apoptosis

Apoptosis is a programmed cell death cascade involved in several physiological processes during development and aging. Cell death by apoptosis sustains the homeostasis of cell population in tissues including cell turnover, hormone dependent- and chemical induced-cell death, and immune system development. The programmed cell death also functions as a defense when cells are damaged by disease or noxious stimuli (Elmore, S; 2007). Thereby, inappropriate apoptosis is a potential mechanism implicated in the pathogenesis of several neurodegenerative disorders, including ALS (Elmore, S; 2007). There are two main apoptotic pathways, the extrinsic or death receptor pathway and the intrinsic or mitochondrial pathway (Igney and Krammer, 2002). The extrinsic pathway involves transmembrane receptor-mediated interactions between ligands and death receptors resulting in transmission of death signals from cell surface to the intracellular signaling pathways (Locksley et al., 2001). The most studied ligand and death receptor association are Fas ligand and Fas receptor (FasL/FasR) and tumor necrosis factor (TNF) and its receptor (TNFL/TNFR) (Hsu et al 1995; Wajant, 2002). The intrinsic pathway consists of non-receptor-mediated stimuli that cause changes in the inner mitochondrial membrane. These changes include the opening of mitochondrial membrane pores leading to loss of transmembrane potential and released of pro-apoptotic proteins such as cytochrome c, Smac/DIABLO, HtrA2/Omi, and others ending with the activation of caspases (Sealens, et al., 2004; Du et al., 2000; Van Loo et al., 2002; Garrido at al., 2005). The

Bcl-2 family of proteins regulates the intrinsic apoptotic pathway (Cory and Adams 2002) and these proteins in turn are regulated by the tumor suppressor protein p53 (Schuler and Green, 2001). The Bcl-2 family includes pro-apoptotic and anti-apoptotic proteins. Some of the anti-apoptotic proteins comprise Bcl2, Bcl-x, Bcl XL, Bcl-XS, Bcl-w, BAG, whereas the pro-apoptotic proteins include Bcl-10, BAX, Balk, Bid, Bad, Bim, Bik, and Blk. Both the intrinsic and extrinsic pathways require a specific stimuli to activate its own caspase initiator (caspase -2,-8,-9,-10). These two pathways, once activated, convey in the activation of a final execution pathway with cleavage of caspase-3, resulting in DNA fragmentation, cytoskeletal and nuclear protein cleavage, protein cross-linking, apoptotic bodies formation, expression of ligands for phagocytic recognizion, and final uptake by phagocytic cells (Martinvalet, et al, 2005). There is compelling evidence in ALS, at least in mutant SOD1-ALS, that toxicity is mediated by apoptosis. In transgenic SOD1 mice there are numerous apoptotic findings such as DNA fragmentation, caspase activation, and altered expression of the anti-apoptotic protein Bcl-2 (Durham HD, et al. 1997; Spooren WP et al. 2000). Motor neuron degeneration in ALS structurally resembles apoptosis. The neuronal death progression is divided in 3 sequential stages: chromatolysis, somatodendritic attrition, and apoptosis. In ALS, in the spinal cord anterior horn and motor cortex there is DNA fragmentation and increased in caspase-3 activity. Vulnerable central nervous system regions affected by ALS show elevation of pro-apoptotic proteins Bax and Bak and reduction of the antiapoptotic protein Bcl-2 in mitochondrial-enriched membrane compartment. Co-immunoprecipitation experiments show greater Bax-Bax interactions and lower Bax-Bcl-2 interactions in the mitochondrial-enriched membrane compartment of ALS motor cortex compared with controls, (Martin LJ, 1999). In mutant SOD1 mice apoptotic signals are activated in sequence, caspase 1, an inflammatory caspase, is activated at disease onset while activated caspase-3 is detected later in the curse of the disease (Pasinelli, P, et al. 2000). In SOD1 mice, intracerebroventricular injection of a broad caspase-inhibitor reduces caspase 1 and caspase 3 mRNA levels resulting in spear motor neurons at the spinal cord and delay in disease onset and progression compared with vehicle-infused mice (Li M, et al.; 2000). Overexpression of the antiapoptotic protein Bcl-2 and deletion of the pro-apoptotic protein Bax preserve motor function and prolong life in a $SOD1^{G93A}$ model. Genetic deletion of mitochondrial pro-apoptotic Bak and Bax proteins in a mouse model of ALS prevent neuronal loss and axonal degeneration, and delayed onset of disease (Reyes et al., 2012).

In $SOD1^{G93A}$ transgenic mice, cytosolic release of cytochrome c was observed (Pasinelli, et al., 2004; Kirkinezos et al., 2005; Takeuchi et al., 2002), and levels of pro-apoptotic proteins Bad and Bax were increased while those of anti-apoptotic proteins Bcl2, Bcl-xL and XIAP were decreased (Guegan et al., 2001; Vukosavic et al., 1999; Ishigaki et al., 2002). Caspase 1 and caspase 3 were also sequentially activated in motor neurons and astrocytes in $SOD1^{G93A}$, $SOD1^{G37R}$, and $SOD1^{G85R}$ mice (Li et al., 2000; Pasinelli et al., 1998; Pasinelli et al., 2000). Intraventricular administration of minocycline, which inhibits cytochrome c release from mitochondria, was shown to delay disease onset and extend survival (Zhu et al., 2002). However minocycline failed in human ALS patients (Gordon et al, 2007). Similar results were observed upon intraventricular administration of the broad-spectrum caspase inhibitor zVAD-fmk (Li et al., 2000). Additionally, over-expression of anti-apoptotic protein Bcl-2 delayed

activation of the caspases, attenuated neuron degeneration and delayed disease onset and mortality (Vukosavic et al., 1999, Kostic et al., 1997).

11. Conclusion

The research in the ALS field encounters many limitations, what is clearly reflected in the little progress accomplished in the therapy of this neurodegenerative disorder. Most of the studies describe the mechanisms involved in the pathogenesis of the familial form of ALS, which accounts for a minority of all the ALS cases. However, some of the hypothesis currently under investigation may also explain how the pathology develops in the sporadic forms of ALS. In the last two decades several experimental models *in vitro* and *in vivo* have shaded light into the pathogenesis of the disease. Several potential mechanisms have been implicated in ALS onset and progression including oxidative stress, excitotoxicity, mitochondrial dysfunction, glial activation, RNA-processing, and growth factor abnormalities. Whether these mechanisms intertwine, work in parallel or in sequence to cause neuronal death remains to be investigated.

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