

## Review

## Calcium-dependent protein folding in amyotrophic lateral sclerosis

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## ABSTRACT

Amyotrophic lateral sclerosis is a neurodegenerative disease characterized by a progressive loss of motor neurons. Although the etiology remains unclear, disturbances in  $\text{Ca}^{2+}$  homeostasis and protein folding are essential features of neurodegeneration. The correct folding of proteins is managed by folding proteins, which are regulated by  $\text{Ca}^{2+}$  levels. Therefore,  $\text{Ca}^{2+}$ -sensitive folding proteins represent an important link between disturbed  $\text{Ca}^{2+}$  handling and protein misfolding in amyotrophic lateral sclerosis. In the first part of this review, we focus on  $\text{Ca}^{2+}$  handling in the endoplasmic reticulum and mitochondria in terms of their roles in protein misfolding. In the second part, we draw attention to the main  $\text{Ca}^{2+}$ -sensitive folding proteins that play a role in motor neuron degeneration such as calreticulin and calnexin, which are involved in the folding of glycosylated proteins. In addition, calmodulin and the  $\text{Ca}^{2+}$ /calmodulin-dependent protein kinase are discussed as one correlation to oxidative stress. The heat shock protein endoplasmic reticulum chaperone is associated with the anti-apoptotic insulin-like growth factor pathway that is altered in amyotrophic lateral sclerosis. Grp78, which influences  $\text{Ca}^{2+}$  homeostasis in the intraluminal endoplasmic reticulum is upregulated in mice models and amyotrophic lateral sclerosis patients and constitutes a core component of the unfolded protein response. Lastly, the protein disulfide isomerase family is responsible for mediating oxidative protein folding in the endoplasmic reticulum.

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## 1. Introduction

Protein misfolding and the ensuing cellular responses are common features of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). As the most common adult-onset motor neuron disease, ALS is characterized by upper (spasticity, dysphagia, dysarthria) and lower motor neuron (atrophy, fasciculations) degeneration. Approximately 90% of ALS patients have sporadic ALS (sALS) which is the most prevalent form and about 10% have the inherited or familial form of ALS (fALS). The latter form is believed to be due to several genes including SOD1, TARDBP, FUS, OPTN, VCP. In addition, a hexanucleotide (GGGGCC) repeat expansion in the first intron of the C9ORF72 gene [1,2] has also lately been demonstrated as being associated with ALS. However, the etiology of the disease is still unclear, although recent studies indicate that  $\text{Ca}^{2+}$  disturbances, endoplasmic reticulum (ER) stress, and mitochondrial dysfunction are involved in the pathogenesis of ALS [3,4]. The ER is a continuous network of membranes housing many functions critical to cellular survival [5]. Since an important

function of the ER is the intracellular storage of  $\text{Ca}^{2+}$ , the ER is involved in initiating/instigating cytosolic  $\text{Ca}^{2+}$  signals and plays a major role in signalling pathways. Many of these functions are dependent on proteins, acting as  $\text{Ca}^{2+}$  buffers and also as molecular chaperones, a process relevant to protein folding and protein quality control. Since these folding functions depend on ER intraluminal  $\text{Ca}^{2+}$  concentration [6–8], a disturbance in the ER mitochondrial  $\text{Ca}^{2+}$  cycle (ERMCC) influences ER function and its role in protein synthesis and folding, including post-translational modifications which lead to ER stress and to activation of the unfolded protein response (UPR) [4,5,9].

This review focuses on the interaction between  $\text{Ca}^{2+}$  and protein folding in ALS. The  $\text{Ca}^{2+}$ -modified folding proteins are seen as a link between the observed  $\text{Ca}^{2+}$  disturbance and protein misfolding. In addition, the protein folding mechanism itself is of significance due to its role as a potential therapeutic target in ALS.

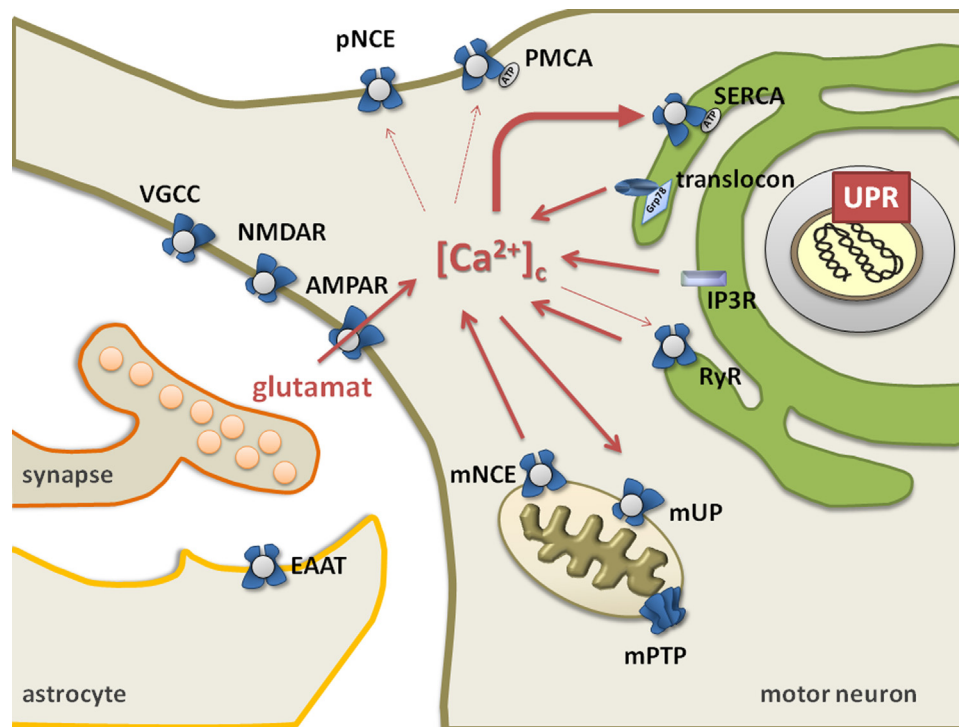
2. Physiology of  $\text{Ca}^{2+}$  handling in ER and mitochondria

The ER and mitochondria form a highly dynamic interconnected network that is involved in the generation of  $\text{Ca}^{2+}$  signals. During normal signalling, there is a continuous ebb and flow of  $\text{Ca}^{2+}$  between the ER and mitochondria [8].  $\text{Ca}^{2+}$  release from ER is controlled by ryanodine receptors (RyRs,  $\text{Ca}^{2+}$ -gated  $\text{Ca}^{2+}$  channels) [10,11], the inositol 1,4,5-triphosphate receptor-gated channels

Abbreviations: ALS, amyotrophic lateral sclerosis; ER, endoplasmic reticulum; ERMCC, endoplasmic reticulum-mitochondria- $\text{Ca}^{2+}$  cycle; NO, nitric oxide; SOD, superoxide dismutase; UPR, unfolded protein response.

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**Fig. 1.** The endoplasmic reticulum–mitochondria–Ca<sup>2+</sup> cycle (ERMCC). Ca<sup>2+</sup> can enter cytosol through: the AMPA receptor, the ryanodine receptor (RyR) at the ER membranes, the opening of the inositol 1,4,5 trisphosphate receptor (IP3R), the translocon at the ER membrane, and/or the plasmalemmal voltage gated Ca<sup>2+</sup> channels (VGCC). Triggered by physiological activity of AMPA receptors with pathologically increased Ca<sup>2+</sup>-permeability in ALS, a chronic shift of Ca<sup>2+</sup> from the ER to the mitochondria (i.e. through Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release through RyR and mitochondrial uptake through the uniporter mUP) causes depletion of ER Ca<sup>2+</sup> levels with protein misfolding (UPR) and chronic mitochondrial Ca<sup>2+</sup> overload. Cytosolic Ca<sup>2+</sup> clearance is facilitated by the plasma membrane Ca<sup>2+</sup> ATPase, the plasmalemmal Na<sup>+</sup>/Ca<sup>2+</sup> exchanger (NCE), the sarco/endoplasmic reticulum Ca<sup>2+</sup> ATPase (SERCA), and the Golgi apparatus. Astrocytes control the level of persisting glutamate at the glutamatergic synapse through glutamate transporters (EAAT), but also exert life-supporting functions in motor neurons (i.e. BDNF, IGF, VEGF). (NMDAR = NMDA receptors, VGCC = voltage gated Ca<sup>2+</sup> channels, Na/K = Na<sup>+</sup>/K<sup>+</sup> pump, pNCE = plasmalemmal Na<sup>+</sup>/Ca<sup>2+</sup> exchanger, PMCA = plasmalemmal Ca<sup>2+</sup> ATPase, mNCE = mitochondrial Na<sup>+</sup>/Ca<sup>2+</sup> exchanger, SERCA = sarco-endoplasmic Ca<sup>2+</sup> ATPase). Figure adapted from [4].

(IP3Rs), and the translocon [12,13]. Restocking of the ER with Ca<sup>2+</sup> is executed by the sarco/endoplasmic reticulum Ca<sup>2+</sup>-ATPase (SERCA) [9,14,15]. The housekeeping SERCA2b Ca<sup>2+</sup> pump serves a dual role. It restores the cytosolic Ca<sup>2+</sup> concentration to its low resting level (100 nM) and maintains a high (500 μM) luminal ER Ca<sup>2+</sup> concentration [16]. Ultimately, the sodium/Ca<sup>2+</sup>-exchanger and plasma membrane Ca<sup>2+</sup> ATPase remove Ca<sup>2+</sup> from the cell [17] (Fig. 1).

Mitochondria take up Ca<sup>2+</sup> via a Ca<sup>2+</sup>-sensitive electrogenic carrier (mUP) which is gated by cytosolic Ca<sup>2+</sup> in a biphasic-dependent manner [18]. Ca<sup>2+</sup> uptake into mitochondria is facilitated by Ca<sup>2+</sup>/calmodulin. However, sustained cytosolic Ca<sup>2+</sup> levels inactivate the uniporter, preventing further Ca<sup>2+</sup> uptake [19]. Accumulated Ca<sup>2+</sup> in the mitochondria can slowly be ejected back into the cytosol through Na<sup>+</sup>/Ca<sup>2+</sup> and 2H<sup>+</sup>/Ca<sup>2+</sup> exchangers [20] (Fig. 1). Once intramitochondrial Ca<sup>2+</sup> rises above a certain threshold, the voltage- and Ca<sup>2+</sup>-dependent high-conductance channel in the inner membrane, known as the mitochondrial permeability transition pore (mPTP) opens leading to cell death either by apoptosis or necrosis [21,22].

Because the maximal Ca<sup>2+</sup> release rate is lower than the maximal uptake, a continuous mitochondrial Ca<sup>2+</sup> accumulation is observed when cytosolic free Ca<sup>2+</sup> rises above the set-point of 0.5 μmol/l [20]. Mitochondria contain low Ca<sup>2+</sup> levels as resting cells, but accumulate a considerable amount during stimulated Ca<sup>2+</sup> entry which affects numerous cellular processes such as cellular energy metabolism, synaptic transmission and excitability, intracellular signalling, generation of ROS, and activation of apoptosis [23,24].

### 3. Disturbance of Ca<sup>2+</sup> homeostasis and protein folding in ALS

#### 3.1. The endoplasmic reticulum–mitochondria–Ca<sup>2+</sup> cycle (ERMCC) in ALS

Several studies have previously investigated abnormalities of Ca<sup>2+</sup> homeostasis, ER and mitochondrial abnormalities as well as excitotoxicity in motor neurons in ALS [4,25]. Based on the models described by Berridge [5], a persistent shift of Ca<sup>2+</sup> from the ER to mitochondria (i.e. through Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release via RyR and mitochondrial uptake through mUP) was postulated. This could be triggered by the physiological activity of AMPA receptors together with a pathologically increased Ca<sup>2+</sup>-permeability [4]. This, in turn, leads to a depletion of Ca<sup>2+</sup> levels in the ER resulting in protein folding dysfunction and chronic mitochondrial Ca<sup>2+</sup> overload. Both protein misfolding and Ca<sup>2+</sup> overload can then induce apoptosis through Bcl-2 dependent mechanisms [4]. Since the Ca<sup>2+</sup> appears to be shuttled back and forth between the ER and the mitochondrial compartment, the process has been termed the ER–mitochondria Ca<sup>2+</sup> cycle (ERMCC, Fig. 1) [4].

There are several factors which contribute to the selective vulnerability of motor neurons in ALS. Clearly, due to their intrinsic properties, motor neurons are extremely vulnerable to glutamate excitotoxicity via AMPA receptors. The ALS-vulnerable motor neurons, possess a large number of Ca<sup>2+</sup>-permeable receptors lacking the GluR2 subunit, making them highly permeable to Ca<sup>2+</sup> compared to the more resistant neurons such as the oculomotor neurons [26]. Conversely, ALS-vulnerable motor neurons have low

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