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Critical review

The role of *SIGMAR1* gene mutation and mitochondrial dysfunction in amyotrophic lateral sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) patients exhibit diverse pathologies such as endoplasmic reticulum (ER) stress and mitochondrial dysfunction in motor neurons. Five to ten percent of patients have familial ALS, a form of the disease caused by mutations in ALS-related genes, while sporadic forms of the disease occur in 90–95% of patients. Recently, it was reported that familial ALS patients exhibit a missense mutation in *SIGMAR1* (c.304G > C), which encodes sigma-1 receptor (Sig-1R), substituting glutamine for glutamic acid at amino acid residue 102 (p.E102Q). Expression of that mutant Sig-1R^{E102Q} protein reduces mitochondrial ATP production, inhibits proteasome activity and causes mitochondrial injury, aggravating ER stress-induced neuronal death in neuro2A cells. In this issue, we discuss mechanisms underlying mitochondrial impairment seen in ALS motor neurons and propose that therapies that protect mitochondria might improve the quality of life (QOL) of ALS patients and should be considered for clinical trials.

1. Amyotrophic lateral sclerosis and mitochondrial dysfunction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder with upper and lower motor neuron deficits. This disease affects an estimated 1–2 individuals per 100,000 every year. ALS can be manifested by muscle weakness and atrophy, fasciculations, paralysis, swallowing disorders and respiratory dysfunction. Symptoms progress rapidly after disease onset, and half of all patients die within 3–5 years (1). ALS is classified as sporadic (SALS; ~90–95%) or familial (FALS; ~5–10%) (2,3). The cause of SALS is largely unknown but assumed to include genetic and environmental factors, while, genetic factors underlying FALS have been reported and account for approximately 70% of those cases (4). One dominant mutation in the *superoxide dismutase 1* (*SOD1*) gene was first identified in FALS patients, and so far, over one hundred *SOD* mutations have been defined (4,5). SOD1 functions in removal of reactive oxygen species (ROS) that induce mitochondrial dysfunction and apoptosis (6). In fact, spinal motor neuron loss is a major pathology seen in ALS patients and, model mice (7). Transgenic model mice harboring the human SOD1^{G93A} mutation have been extensively analyzed, greatly enhancing our understanding of ALS pathology. Most SOD1 mutations are associated with loss of its enzymatic activity; however, in contrast to SOD1^{G93A}model mice, SOD1 null mice exhibit normal motor neuron development and function until they are at least until 6 months old, suggesting that SOD1 loss of function is not a direct cause of ALS onset (8,9).

SOD1^{G93A} mutant protein localizes to mitochondria by forming a complex with Bcl-2 (10,11). Bcl-2 functions to inhibit apoptosis by regulating both cytochrome c release from mitochondria and caspase activation. Pasinelli et al reported that SOD1^{G93A} forms aggregates with Bcl-2 in the spinal cord but not in the liver of model mice (11). This is an interesting observation because Bcl-2 null mice show degeneration of motor, sensory and sympathetic neurons (12). By contrast, genetic deletion of either the pro-apoptotic factors Bax or Bak in SOD1^{G93A} mice inhibits motor neuron degeneration and promotes mouse survival (13). Similarly, perturbed ER-mitochondria interaction was observed in embryonic motor neurons from SOD1^{G93A} mutant mice (14). Taken together,

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mitochondria-induced apoptosis underlies ALS pathogenesis promoted by SOD1^{G93A}.

Mitochondria are also crucial for regulation of cell calcium homeostasis and energy production through the tricarboxylic acid (TCA) cycle, the electron transport chain and ATP synthase. Both mitochondrial fission and fusion are impaired in ALS patients. Mitochondrial fission/fusion directly or indirectly influence mitochondrial energy metabolism. Knock-out or down-regulation of fission or fusion proteins reduces mitochondrial respiration and ATP generation (15). In addition, decreased mitochondrial calcium transport through the mitochondrial calcium uniporter (MCU) is observed in brainstem neurons of aging SOD1^{G93A} mice (16). Consistent with these findings, levels of stored mitochondrial calcium decline in these neurons (17). However, mechanisms underlying mitochondrial impairment due to expression of ALS-related genes are largely unknown.

Sig-1R is an ER-resident chaperone protein that localizes predominantly to the mitochondrial-associated ER membrane (MAM), where Sig-1R stimulation promotes calcium transport into mitochondria through the IP_3 receptor (18). Indeed, IP_3 production following stimulation of G protein-coupled receptors (GPCRs) enhances mitochondrial calcium transport and ATP production in neurons and cardiomyocytes (19, 20). Furthermore, the physiological relevance of Sig-1R in neuropsychotherapeutic drug actions is well documented in the current issue (21,22). The pathophysiological relevance of Sig-1R in neurodegenerative disorders and ALS is also extensively discussed in the present issue (23,24). Recently, a missense mutation in *SIGMAR1* causing substitution of glutamine for glutamic acid at Sig-1R amino acid residue 102 (p.E102Q) was reported in juvenile FALS patients (25). To determine whether ALS-related *SIGMAR1* mutations cause mitochondrial impairment in neurons, we transfected neuro2A cells with a construct encoding either wild-type Sig-1R or the p.E102Q mutant (Sig-1R^{E102Q}) and assessed mitochondrial function (26). Sig-1R^{E102Q} mutant caused dissociation of Sig-1R^{E102Q} proteins from the ER membrane and its subsequent cytoplasmic aggregation (Fig. 1A). We also observed disrupted mitochondrial structure following Sig-1R^{E102Q} expression, as assessed by cytochrome c staining, an effect not seen after expression of the wild-type protein. Mitochondrial damage preceded autophagic cell death, as assessed by LC3-II formation (26). Aberrant mitochondrial morphology is associated with reduced ATP production. ATP is required not only for cell metabolism but

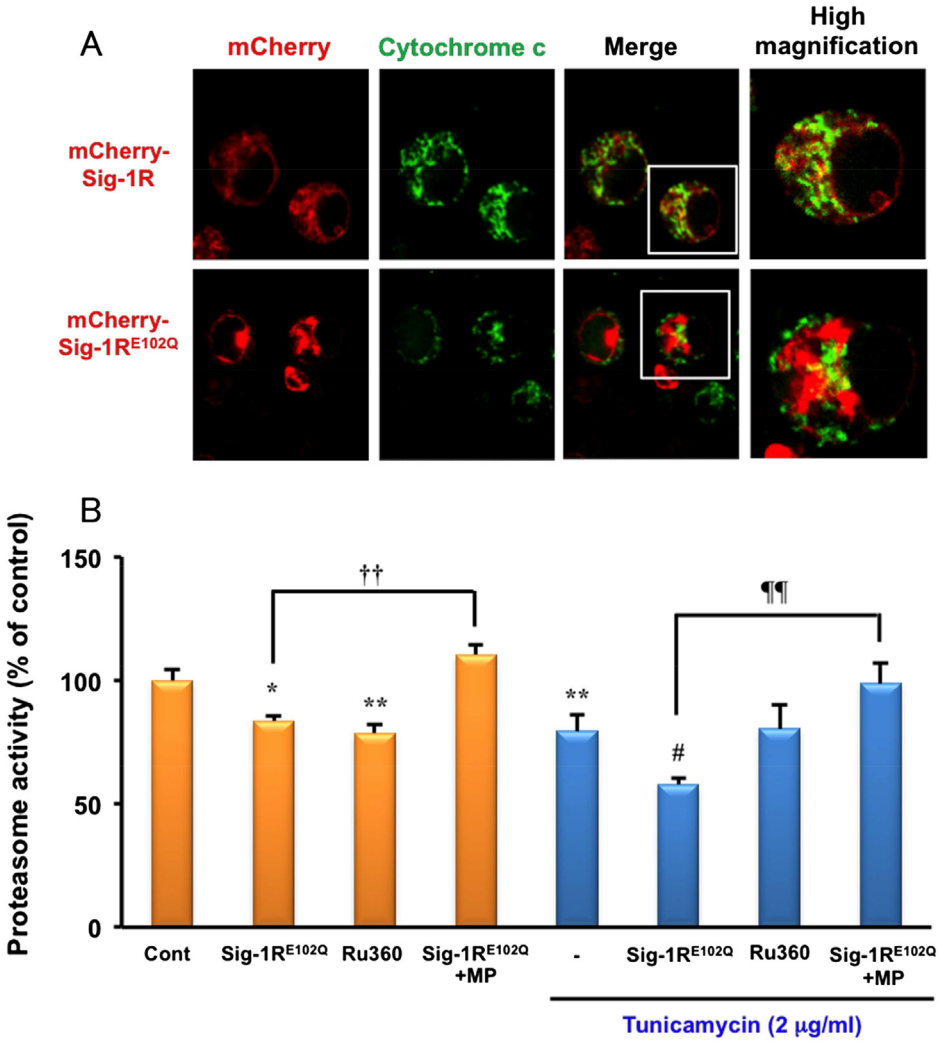

Fig. 1. Intracellular localization of overexpressed Sig-1R- or Sig-1R^{E102Q}-mCherry proteins in transfected Neuro2A cells. (A) Immunofluorescence showing intracellular localization of Sig-1R or Sig-1R^{E102Q} (red) and the mitochondrial marker cytochrome c (green). **(B)** Measurement of proteasome activity with or without tunicamycin (2 μg/ml), methyl pyruvate (MP) or Ru360 for 48 h. Each column represents the mean ± S.E.M. *, $P < 0.05$ and **, $P < 0.01$ versus control cells (Cont); #, $P < 0.05$ versus tunicamycin-treated cells; ††, $P < 0.01$ versus Sig-1R^{E102Q}-transfected cells; ¶¶, $P < 0.01$ versus σ_1RE102Q-transfected and tunicamycin-treated cells. Modified from (20).

also for proteasome activity. Indeed we found that ATP reduction neuro2A cells led to reduced proteasome activity, especially under ER stress conditions such as tunicamycin treatment (Fig. 1B). Likewise, treatment of neuro2A cells with Ru360, a mitochondrial calcium uniporter inhibitor, reduced both ATP production and proteasome activity (Fig. 1B). Treatment of neuro2A cells with methyl pyruvate (MP), which increases ATP production, totally rescued proteasome activity, even under ER stress conditions (26). Moreover, σ_1R^{E102Q}-overexpressing cells showed aberrant extra-nuclear localization of the TAR DNA-binding protein (TDP-43), a condition exacerbated by tunicamycin-dependent ER stress (Fig. 2) and partly due to reduced mitochondrial Ca^{2+} transport and ATP production. TDP-43 extra-nuclear localization was also associated with formation of cellular inclusion bodies and TDP-43 hyper-ubiquitination (26) (Fig. 3). However, it is remains unclear whether or how TDP-43 extra-nuclear localization promotes mitochondrial damage seen in ALS patients.

TDP-43-positive inclusions in the cytosol of motor neurons have been observed in almost all ALS patients (27). TDP-43 was first identified as a protein binding to the human immunodeficiency virus type-1 (HIV-1) long terminal repeat (TAR), thereby regulating HIV-1 gene expression (28). Subsequently, two groups simultaneously reported the appearance of aberrant TDP-43-positive cytosolic inclusions and skein-like inclusions in the spinal cord, hippocampus and neocortex in tissue samples from patients with frontotemporal lobar degeneration (FTLD) and in the spinal cord of ALS patients (29,30). Those investigators also documented that TDP-43 is subject to posttranslational modifications, such as hyperphosphorylation, ubiquitination or cleavage of its C-terminal fragments. In 2008, investigators reported TDP-43 mutations in FALS and SALS patients (31). TDP-43 exhibits both a nuclear localization signal and a nuclear export signal, enabling it to shuttle between the nucleus and cytosol. It also harbors a glycine-rich region serving as prion-like domain in its C-terminus, where most pathological mutations reside. Physiological functions of TDP-43 include: i) translational repression, ii) regulation of splicing, iii) RNA transport and formation of stress granules through binding with the 3′UTR of RNA, and iv) regulation of microRNA activity (27). Genome-wide RNA immunoprecipitation analysis revealed that TDP-43 binds at least 6000 RNA targets and can occupy more than 40,000 RNA binding sites in brain (27). Moreover, TDP-43 knockdown by RNA interference *in vivo* alters expression of over 600 RNAs and splicing of over 950 in mouse brain (32). Among them, genes down-regulated following TDP-43 knockdown include those encoding the L-type voltage-dependent calcium channel, IP_3 receptor type 1, ryanodine receptor 2 and calcium/calmodulin-dependent protein kinase IV, all associated with synaptic transmission and/or calcium homeostasis (32, 33). Genes up-regulated following TDP-43 knockdown function in lysosomal degradation, which is associated with immune defense and inflammatory systems (32). Overexpression of TDP-43^{Q331K} or TDP-43^{M337V} mutants in rat primary motor neurons results in shortening of mitochondria in dendrites and axons, cell compartments also exhibiting abnormal mitochondrial transport (34). Interestingly, TDP-43^{Q331K} or TDP-43^{M337V} mutant proteins preferentially co-localize with mitochondria in axons and dendrites unlike nuclear localization of wild-type TDP-43 protein, suggesting that TDP-43 mutants likely bind to mitochondria in neurons (34). Moreover, wild-type TDP-43, TDP-43^{Q331K} or TDP-43^{M337V} overexpressed in cells of the motor neuron line NSC-34 localizes to mitochondrial membranes and promotes reduction in mitochondrial membrane potential and complex I activity. Mitochondrial localization of TDP-43 is closely

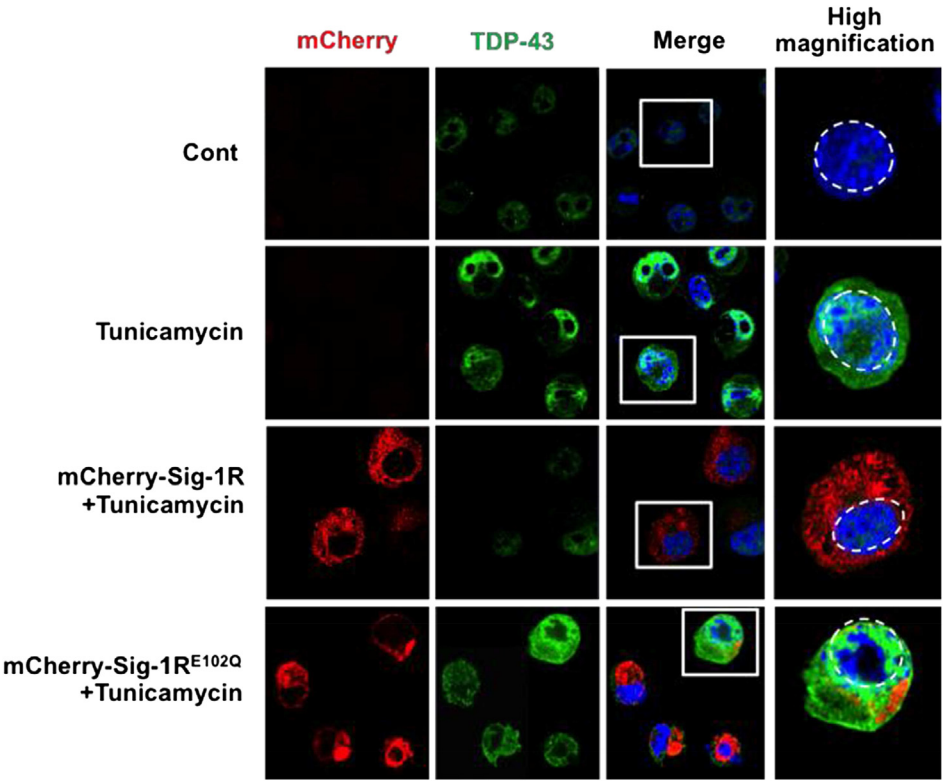

Fig. 2. Effect of tunicamycin treatment and Sig-1R^{E102Q} overexpression on TDP-43 mislocalization. Confocal analyses were carried out with or without transfection of Sig-1R or Sig-1R^{E102Q} (red) in the presence or absence of tunicamycin (ER stress inducer) in Neuro2A cells. Cells were also stained with TDP-43 antibody (green) and DAPI (blue). Modified from (20).

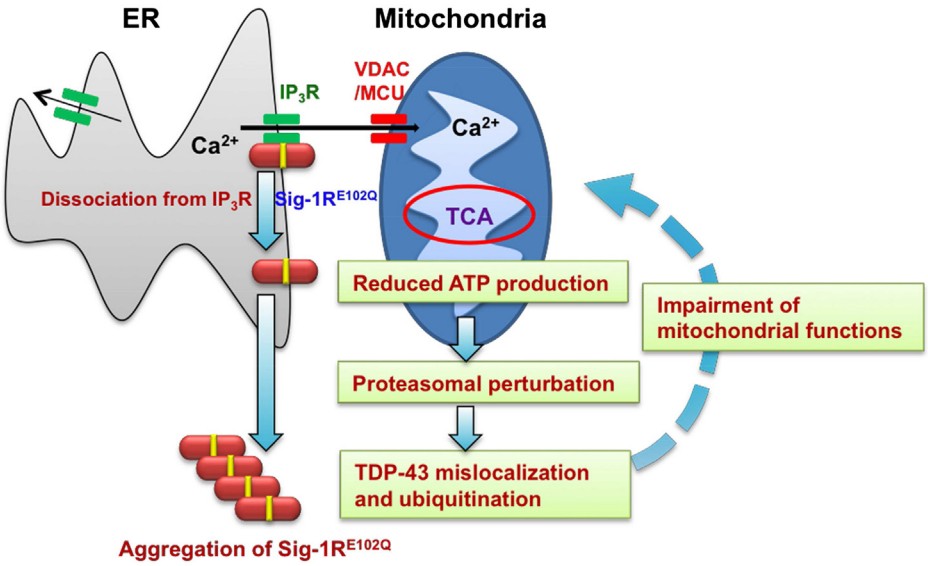

Fig. 3. Working hypothesis Sig-1R^{E102Q} mutant in ALS pathology. Under ER stress conditions, Sig-1R^{E102Q} dissociates from the ER and aggregates in the cytoplasm. Loss of the Sig-1R/IP$_3$R association impairs mitochondrial Ca^{2+} transport, reduces Ca^{2+}-dependent ATP production and disturbs proteasome activity. Mislocalization and hyper-ubiquitination of TDP-43 in the cytosol may further impair mitochondrial and autophagosome function. IP$_3$R3: IP$_3$ receptor type 3, TDP-43: TAR DNA-binding protein. Modified from (20).

related to ROS generation and mitophagy in NSC-34 cells (35,36). Furthermore, NSC-34 cells overexpressing TDP-35 and TDP-25, which are respective 35 and 25 kDa C-terminal fragments of TDP-43, show co-localization of the mutant protein with mitochondria and mitochondrial dysfunction and mitophagy (35). Membranes of the ER and mitochondria are closely associated via protein–protein interactions between Mfn1/Mfn2 or VAPB/PTPIP51 (37,38). Stoica et al. reported that overexpression of wild-type or TDP-43 mutants (M337V, Q331K, A382T and G348C) in NSC-34 cells interferes with VAPB/PTPIB51 interaction and disrupts ER-mitochondria junctions. These activities also occur in motor neurons of TDP-43-overexpressing transgenic mice (39). Transgenic mice overexpressing either wild-type or mutant forms of TDP-43 show abnormal cytoplasmic localization of phosphorylated and ubiquitinated inclusions in neurons of the spinal cord, cortex and hippocampus (40–43). Like SOD1^{G93A} mice, transgenic mice overexpressing wild-type or mutant TDP-43 also exhibit mitochondrial aggregation in spinal motor neurons (40,41). Similarly, in mice, knock-in of the human TDP-43^{A315T} mutant promotes formation of ubiquitin-positive inclusion bodies containing TDP-43 in the spinal cord and abnormal mitochondrial structure in motor cortex neurons (44). Taken together, aberrant cytosolic localization of either wild-type or mutant forms of TDP-43 directly impairs mitochondrial function.

2. Aberrant mitochondrial function in other ALS models

Ferri et al. has reported that SOD1^{G93A} overexpression, but not overexpression of wild-type SOD1, in NSC-34 cells induces mitochondrial fragmentation associated with both up-regulation of mitochondrial fission protein Drp1 and down-regulation of fusion protein Opa1 (45). SOD1^{G93A} expression also induced aberrant mitochondrial macrostructure, such as swelling, abnormal cristae and vacuolization, in NSC-34 cells (46). Dominant mutations in other genes including *TAR DNA-binding protein 43* (*TARDBP*), *FUS RNA-binding protein* (*FUS*), *ubiquilin 2* (*UBQL2*), *sequestosome 1* (*SQSTM1, p62*), and *optineurin* (*OPTN*) are causative of FALS (31,47–51). Like TDP-43, FUS is DNA/RNA binding proteins regulating RNA translation, splicing and stability. Transgenic rats harboring human *FUS*, as well as *TARDBP* transgenic mice, reportedly show aggregation of abnormal mitochondria in entorhinal cortical neurons (52). *UBQL2* and *SQSTM1* gene products regulate proteasomal and autophagic degradation of ubiquitinated proteins, respectively (53,54). *OPTN* and *SQSTM1* gene products function in mitochondrial quality control by regulating degradation of damaged mitochondria. Wong and Holzbaur also reported that the wild-type *OPTN* gene product, but not its ALS-related mutant E478G, localizes to mitochondria following mitochondrial depolarization, suggesting that removal of impaired mitochondria is dysregulated in ALS (55).

3. Disease-modifying ALS therapies

Pre-clinical studies targeting mitochondria and oxidative stress have been carried out using the SOD1^{G93A} model mice, and several potential therapeutics have been proposed (56–58). Riluzole, the only agent approved to treat ALS in Japan, is thought to exert a neuroprotective effect by blocking voltage-dependent cation channels, preventing neuronal hyperactivity and glutamate excitotoxicity (59). However, riluzole effects are limited as prolonging survival for only a few months, and the drug has little effect in delaying or ameliorating symptoms. Thus, disease-modifying therapeutics are still required to improve QOL of patients. We have noted that Sig-1R null mice aggravate neuropathology in SOD1^{G94A} mice, thereby reducing longevity of the mice (60). In motor neurons, subsurface cisternae of the ER, a region where Sig-1R interacts with IP$_3$R type 3, show enrichment in Sig-1R. Calcium release from IP$_3$R may promote conductance of potassium channels such as small conductance calcium-activated potassium channels (SK) channels (61). Those authors proposed that the loss of Sig-1R-regulated SK channel activation in Sig-1R null mice increases motor neuron excitability, leading to cell death. These experiments also suggest that Sig-1R agonists could have beneficial effects for ALS patients. As expected, administration of the Sig-1R agonist PRE-084 (0.25 mg/kg) to 8 to 16-week-old SOD1^{G94A} mice significantly extended their survival by more than 15% and delayed disease onset in both male and female mice. Extended motor neuron survival was associated with protein kinase C-dependent

phosphorylation of the NR1 subunit of the NMDA receptor and decreased microglial activity (62). Similarly, Peviani et al. reported that chronic treatment of mice with PRE-084, starting at symptom onset, significantly increased levels of brain-derived neurotrophic factor (BDNF) in gray matter and improved motor neuron survival (63). PRE-084 treatment was also associated with reduction in the number of reactive astrocytes and increases in $CD11b^{+}$ microglial cells. These findings were confirmed by treatment of $SOD1^{G94A}$ mice with a different Sig-1R agonist, SA4503 (64). Given that mitochondrial damage likely underlies neurodegeneration seen in ALS, therapy that rescues that damage could constitute potential therapy. To test this hypothesis, we treated cultured neuro2A cells overexpressing Sig-$1R^{E102Q}$ with methyl pyruvate (5 μM) as a substrate of TCA cycle (26) and observed rescued ATP production, which is down-regulated in those cells. Notably, similar methyl pyruvate treatment also rescued proteasome activity and extranuclear TDP-43 localization in those cells. Administration of sodium pyruvate (1000 mg/kg/week) from disease onset also extended lifespan of $SOD1^{G94A}$ mice by 12.3 days (65). Although this survival effect was small, combination treatment with both Sig-1R agonists and methyl pyruvate may prove to be more effective and warrants analysis.

4. Conclusion

Sig-1R is a potential therapeutic target in neurodegenerative diseases. Here, we propose that Sig-1R agonists possess potential neuroprotective activity. In ER stress conditions in particular, Sig-1R stimulation promotes mitochondrial Ca^{2+} transport from the ER and mitochondrial ATP production. ATP production may in turn be crucial for proteasome activity, which is essential to degrade abnormal, mislocalized proteins under ER and oxidative stresses. Although Sig-1R agonists would not be beneficial for forms of ALS harboring Sig-1R mutations, combination treatment with Sig-1R agonists and pyruvate could serve as potential therapy for ALS patients. Since clinical trials using sodium pyruvate to treat mitochondrial DNA depletion syndrome are now under way (66) and potent Sig-1R agonists such as fluvoxamine are clinically available (67), these combination therapies to treat ALS could soon be evaluated in the clinical settings.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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