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Mitochondrial dynamic abnormalities in amyotrophic lateral sclerosis

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Abstract

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease characterized by progressive loss of motor neurons in the brainstem and spinal cord. Currently, there is no cure or effective treatment for ALS and the cause of disease is unknown in the majority of ALS cases. Neuronal mitochondria dysfunction is one of the earliest features of ALS. Mitochondria are highly dynamic organelles that undergo continuous fission, fusion, trafficking and turnover, all of which contribute to the maintenance of mitochondrial function. Abnormal mitochondrial dynamics have been repeatedly reported in ALS and increasing evidence suggests altered mitochondrial dynamics as possible pathomechanisms underlying mitochondrial dysfunction in ALS. Here, we provide an overview of mitochondrial dysfunction and dynamic abnormalities observed in ALS, and discuss the possibility of targeting mitochondrial dynamics as a novel therapeutic approach for ALS.

Keywords: ALS, Mitochondrial dysfunction, Mitochondrial dynamics, Mitochondrial fission and fusion, Mitochondrial trafficking, Mitochondrial biogenesis and mitophagy

Introduction

Amyotrophic lateral sclerosis (ALS), also referred to as Lou Gehrig's disease, typically develops between 50 and 60 years of age and progresses rapidly with the average survival of less than 30 months after diagnosis or onset [1]. ALS is the most common motor neuron disease characterized by progressive and fatal degeneration of both upper motor neurons in the motor cortex and lower motor neurons that connect the spinal cord and brainstem to muscle fibers [2], resulting in progressive muscle denervation, loss of motor function, muscle atrophy and eventual paralysis, speech deficit and finally death [3, 4]. Less than 10 % of ALS cases are familial (fALS), of which most are caused by repeat expansions of the C9ORF72 gene or mutations in genes encoding copper–zinc superoxide dismutase (SOD1), TAR DNA binding protein 43 (TDP-43) and fused in sarcoma (FUS). In contrast, 90–95 % of ALS cases, referred to as sporadic ALS (sALS), occur without any family history. The cellular and molecular mechanisms underlying motor neuron degeneration in both fALS and sALS are unknown, and effective treatments for this devastating and fatal disease are extremely limited.

Mitochondria are double membrane-bound organelles that are involved in multiple major cellular processes including ATP production, metabolite synthesis, calcium homeostasis, reactive oxygen species generation and even cell death [5, 6]. Due to limited glycolytic capacity, neurons particularly depend on mitochondria to maintain ion channel activities, synaptic transmission, and axonal/dendritic transport. In addition, as polarized cells with extended axons and dendrites, neurons require mitochondria to be efficiently transported and localized to sites with high metabolic and energy requirements [7]. Not surprisingly, a large number of studies suggest that mitochondria play a critical role in various major neurodegenerative diseases including ALS, Alzheimer's disease, Parkinson's disease and Huntington's disease. Along this line, it was shown that SOD1 encoded by the first discovered gene associated with fALS, was localized to mitochondria [8], and involved in the regulation of mitochondrial function [9–13], underscoring the important role of mitochondria in ALS. In this review, we will focus on mitochondrial dynamic abnormalities in ALS and discuss mitochondrial dynamics as promising therapeutic targets.

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Mitochondrial dysfunction in ALS

Mitochondrial dysfunction has been consistently reported in ALS patients and ALS *in vitro* and *in vivo* experimental models, although the underlying molecular mechanism is still unclear. For instance, decreased activities of oxidative phosphorylation (OXPHOS) complexes I + III, II + III, IV, and citrate synthase were noticed in mitochondria from spinal cords of ALS patients [14, 15]. Consistently, the widely studied SOD1 G93A mouse model of ALS also demonstrated impaired activities of OXPHOS complexes I + III, II + III, IV [9]. Most importantly, mitochondrial dysfunction evidenced by reduced respiration and ATP synthesis precede rather than follow behavioral deficits, indicating an important role of mitochondrial dysfunction in disease progression [9]. Moreover, many ALS associated mutations in SOD1 result in the loss of antioxidant activity and the overproduction of reactive oxygen species (ROS) [16–19], and not surprisingly, a large number of studies reported increased oxidative stress or oxidative damage in spinal cords of ALS patients [20–22]. Elevated Ca^{2+} level in mitochondria was also reported in ALS patients [23] and ALS SOD1 transgenic mouse models [24–26], as as an early event preceding cytosolic Ca^{2+} increase and mutant SOD1 aggregation [27], further supporting the critical role of mitochondrial dysfunction in ALS pathogenesis.

Mitochondrial morphology and fission/fusion dynamics in ALS

Although there is only one study showing abnormal mitochondrial outer membrane protrusions within axons of anterior root in ALS patients using biopsied tissues [28], abnormal mitochondrial morphology has been well documented in ALS experimental models. For example, previous studies from multiple groups showed that mitochondria became fragmented in cell and animal models expressing ALS-associated mutant SOD1 [29–33]. In addtion, we and other groups recently found that ALS-associated mutant TDP-43 overexpression also caused mitochondrial fragmentation in motor neurons *in vitro* and in mice [34–36, 33]. Studies in past decades reveal that mitochondria are highly dynamic organelles, and mitochondrial morphology results from the delicate balance of fission and fusion process [37, 38]. The mitochondrial fragmentation observed in ALS experimental models suggested a tipped balance of mitochondrial fission and fusion towards excessive fission due to increased fission, reduced fusion or both.

Mitochondrial fission and fusion processes are tightly regulated by several large dynamin-related GTPases that exert opposing effects [39]. Mitochondrial fission in mammals involves at least dynamin-like protein 1 (DLP1, also referred to as Drp1) and its recruiting factors on mitochondria such as Fis1, Mff, MiD49 and MiD51 [40]. On the other hand, mitochondrial fusion is governed by three large GTPase proteins: Mitofusin 1 (Mfn1), Mitofusin 2 (Mfn2) and optic atrophy protein 1(OPA1) [41]. Consistent with mitochondrial morphological changes, according to one recent study using SOD1 G93A transgenic mice, the protein levels of fission and fusion regulators including DLP1, Fis1, Mfn1 and OPA1 all increased before disease onset [42]. In contrast, during disease progression, the expression of Mfn1 and OPA1 but not DLP1 and Fis1 were found reduced. Altered expression of mitochondrial fission and fusion regulators such as DLP1 and Mfn1 were also reported in spinal cords of transgenic mice overexpressing wild type TDP-43 [34]. It still remains unknown how the changes in fission and fusion regulators correlate with and contribute to mitochondrial morphological alterations in SOD1 G93A and TDP-43 transgenic mice.

Aside from controlling mitochondrial morphology, mitochondrial fission and fusion dynamics are important for the maintenance of mitochondrial function [43]. Generally, when cells experience metabolic or environmental stresses, fusion enables the exchange of mitochondrial components within the mitochondrial network to compensate for damaged mitochondria, whereas fission helps to create new mitochondria to maintain a healthy mitochondria population [44]. On top of this, a recent study even reported that mitochondrial fission and fusion proteins regulate the assembly of respiratory complexes, indicating the direct involvement of mitochondrial fission and fusion dynamics in mitochondrial bioenergetics [45, 46]. Therefore, it is conceivable that the altered mitochondrial fission and fusion dynamics is likely a mechanism leading to mitochondrial dysfunction in ALS.

Mitochondrial distribution and trafficking in ALS

In neurons, mitochondria are distributed strategically throughout the soma and axons to meet variant energy and metabolism requirements of different compartments. For example, mitochondria are usually found concentrated near synaptic terminals, where synaptic transmission and ion channel activity are highly energy demanding compared with other subcellular regions. However, remarkable mitochondrial accumulation was observed in the soma of motor neurons and proximal axon hillock region in the lumbar spinal cord of ALS patients [47]. Consistently, cultured motor neurons from SOD1 G93A transgenic mice demonstrated abnormal mitochondrial clusters in proximal axons [48]. SOD1 G93A transgenic rats also demonstrated accumulation of mitochondria clustered in axons of motor neurons [49]. Moreover, we and other groups reported altered mitochondrial distribution or mitochondrial aggregation around peri-nuclear area in motor neurons expressing ALS-associated TDP-43 mutant [36, 33, 50, 51].

Since mitochondrial distribution is closely regulated by mitochondrial transportation, one possible cause of abnormal mitochondrial distribution in ALS is altered mitochondrial trafficking, which is increasingly recognized as an important contributor in various neurodegenerative diseases [52, 53]. Mitochondria are transported bidirectionally in neurites along microtubules for fast movement and along actin filaments for slow movement via different motor-adaptor complexes [54]. Mitochondrial transportation is critical for newly generated mitochondria to move from the cell body to reach the distal segments of neurites, and for damaged mitochondria to move from distal neurite compartments to the cell body for degradation [55, 56]. Mitochondrial anterograde movement is mediated by kinesin motors whereas retrograde movement is regulated by dynein motors [57]. Kinesin and dynein motors are indirectly linked to mitochondria by Miro1-Milton adaptor complex [57]. Interestingly, our most recent study found that the expression of Miro 1, the only known mitochondrial outer membrane protein directly coupling mitochondria and motor-adaptor complexes, was significantly reduced in spinal cords of ALS patients, strongly suggesting impaired mitochondrial trafficking in ALS [58]. Consistently, the decreased expression of Miro1 was also noted in spinal cords but not brains of transgenic mice expressing ALS-associated SOD1 G93A or TDP-43 M337V mutant. In fact, we and other groups have provided evidence showing altered axonal transport of mitochondria in motor neurons expressing ALS-associated SOD1 mutant [59, 60] or TDP-43 mutant [36, 33]. Therefore, it is highly possible that Miro-1 deficiency is responsible for mitochondrial movement deficits in ALS and ALS experimental models. However, the possibility of direct interaction between SOD1 or TDP-43 and mitochondrial trafficking machinery can not be ruled out.

Other mitochondrial dynamics in ALS

In addition to fission/fusion and movement, mitochondria function is also sensitive to changes in other mitochondrial dyanmics such as mitochondrial biogenesis and quality control (mitophagy) [61]. Mitochondria biogenesis is regulated by various factors, among which peroxisome proliferation activator receptor gamma-coactivator 1α (PGC-1α) has emerged as the master regulator. PGC-1α is a transcriptional coactivator that regulates the transcription of many genes including NRF1 and NRF2, which control the nuclear genes to encode mitochondrial protein, and TFAM, which drives transcription and replication of mtDNA [62]. It remains to be determined whether mitochondrial biogenesis is changed in ALS patients and experimental models. One study showed there is a loss of mitochondrial mass and reduced expression and activity of SIRT1, a regulator of PGC-1α, in neurons expressing SOD1 G93A mutant [63], suggesting the possible impairment of mitochondrial biogenesis. Damaged mitochondria are usually cleared by the process of mitophagy via mitochondrial quality control systems to maintain a healthy mitochondrial population within cells. The reduced expression of Parkin, an ubiquitin ligase implicated in mitophagy, was observed in transgenic mice expressing ALS associated mutant TDP-43 [64]. An ALS-associated mutation in Optineurin disrupts its function as a receptor for Parkin-mediated mitophagy [65]. In addition, other proteins such as valosin containing protein (VCP, or p97) or p62 were also reported in impairing mitophagy [66, 67]. Along this line, noteworthily, authophagy has been consistently implicated in neuronal loss in transgenic mice expressing ALS associated mutant SOD1 [68–70]. Interestingly, in addition to controlling mitochondrial morphology, previous studies demonstrated that mitochondrial fusion regulator Mfn2 was directly involved in the autophagosome formation [71] and the autophagosome-lysosome fusion [72]. Therefore, further studies might be interesting to test the interplay between autophagy and mitochondrial dynamics in the context of ALS.

Mitochondrial dynamics as therapeutic targets of ALS

The widely used drug for ALS, i.e. riluzole, extends the life span of ALS patients by only three to six months [73, 74] highlighting the need for truly effective treatment options. Increasing evidence has revealed a prominent role for mitochondrial dysfunction in the pathogenesis of ALS and suggest mitochondria as promising therapeutic targets for ALS [75]. For example, SOD1 G93A mice administered CoQ10 in an effort to reduce oxidative stress and improve mitochondria function, demonstrated significantly increased survival [76]. Several chemicals specifically targeting mitochondria such as Olesoxime, Nortriptyline and Cyclosporine were reported as having neuroprotective effects in ALS cell and mouse models [77–80]. In fact, previous studies suggested that altering mitochondrial dynamics including fission/fusion, biogenesis and mitophagy might be viable therapeutic approaches for ALS. For instance, the inhibition of mitochondrial fission by the expression of DLP1 K38A, a dominant negative DLP1 mutant, was reported to prevent ALS-mutant SOD1 induced motor neuronal death [30]. Our recent study showed that the promotion of fusion by overexpression of Mfn2 significantly alleviated ALS-mutant TDP-43 induced mitochondrial and neuronal dysfunction in spinal cord motor neurons [36]. Moreover, resveratrol acting to promote mitochondrial biogenesis was found to significantly improve motor neuron function and extend the lifespan of SOD1 G93A mice [81, 63]. Finally, overexpression of the key biogenesis regulator PGC-1α could also alleviate ALS symptoms in SOD1 G37R transgenic mice [82]. Since mitochondrial function is sensitive to not

only mitochondrial fission/fusion dynamics and biogenesis targeted by these strategies, it will be beneficial to investigate whether the manipulation of mitochondrial trafficking or mitophagy will also have some beneficial effect on mitochondria and neurons in ALS models.

Conclusion

In addition to regulating mitochondrial morphology, mitochondrial fission and fusion are also involved in mitochondrial distribution and movement [83–85]. Further, changes in mitochondrial fission and fusion balance also affect mitophagy [44]. Moreover, PGC-1α was reported to affect mitochondrial morphology. Therefore, these different aspects of mitochondrial dynamics are not isolated but are in fact interrelated mechanisms. This may explain why almost all aspects of mitochondrial dynamics have been reported to be changed in ALS patients and/or ALS models. Notably, SOD1 and TDP-43, the most studied proteins associated with ALS, are found involved in the regulation of mitochondrial dynamics. While it still remains to be determined how altered mitochondrial dynamics contributes to the progression of ALS, like mitochondrial dysfunction, mitochondrial dynamic abnormalities appear to be early features of ALS, suggesting they play a critical role in the pathogenesis of this devastating disease. Supporting this notion, a most recent study showed that impaired mitochondrial trafficking through Miro1 deficiency specifically caused motor neuron degeneration and symptoms of motor neuron diseases [86]. The important role of mitochondrial dynamics in the pathogenesis of a wide range of neurological disorders including ALS, Alzheimer's disease, Parkinson's disease, brain ischemia and epilepsy has been increasingly recognized [87, 3, 88]. Therefore, it is likely that impaired mitochondrial dynamics might be a common mechanism leading to mitochondrial dysfunction and motor neuron degeneration in multiple forms of ALS.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

XW and ZJ wrote the manuscript. WW, GP and XZ provided insightful thoughts into the manuscript. All authors read and approved the final manuscript.

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