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Role of GTPases in the Regulation of Mitochondrial Dynamics in Alzheimer's Disease and CNS-Related Disorders

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Abstract

Data obtained from several studies have shown that mitochondria are involved and play a central role in the progression of several distinct pathological conditions. Morphological alterations and disruptions on the functionality of mitochondria may be related to metabolic and energy deficiency in neurons in a neurodegenerative disorder. Several recent studies demonstrate the linkage between neurodegeneration and mitochondrial dynamics in the spectrum of a promising era called precision mitochondrial medicine. In this review paper, an analysis of the correlation between mitochondria, Alzheimer's disease, and other central nervous system (CNS)-related disorders like the Parkinson's disease and the autism spectrum disorder is under discussion. The role of GTPases like the mfn1, mfn2, opa1, and dlp1 in mitochondrial fission and fusion is also under investigation, influencing mitochondrial population and leading to oxidative stress and neuronal damage.

Keywords Mitochondria · Mitochondrial dynamics · Neurodegenerative diseases · Alzheimer's disease · Parkinson's disease · Oxidative stress

Introduction

Mitochondrion is an organelle with a double membrane-bound which can be found in most eukaryotic cells with several unique characteristics [1]. The number of mitochondria a cell might have can vary widely by the type of the cell, the organism, and the tissues. Mitochondria have a considerable variation in the structure and size in relation to the electrophysiological needs [2, 3]. Mitochondria are intracellular organelles responsible for the supply of adenosine triphosphate (ATP) and play a significant role in life and death of the cell [4]. Mitochondria are responsible for crucial tasks, such as signaling, cellular differentiation, as well as maintaining control of the cell cycle and cell growth [5]. Additionally, mitochondria are critical factors to several human diseases, such as neurodegenerative diseases, where a progressive loss of

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structure or function of neurons occur, including also the death of neurons [6–8]. A large number of factors can affect the mitochondrial geometry, illustrating a more complex problem [9–21], while any morphological change in mitochondrial structure results in electrophysiology problems and biological dysfunctionalities, which are correlated to neurodegenerative disorders [22]. A continuous change in mitochondrial morphologies by fission and fusion independent events leads a mitochondrion to either removal of mitochondrial materials through division or exchange of new materials between mitochondria with the involvement of transport and receptor membrane proteins [23–26]. After a certain number of successful fission and fusion events, there will be a complete, irreversible loss of the initial internal mitochondrial structure, which in turn may limit the matrix and under conditions affect the ATP production [22]. Hence, any failure in fission of the inner mitochondrial membrane can reduce voltage gradient, effect functionality, and generate unstable electric potential [27]. Fission and fusion events are different and independent mechanisms required to maintain mitochondrial functions, and potential disruptions have been reported to promote apoptosis [28] and been involved in aging [29, 30]. During the last decades, several clinical studies and brain tissue testing have already correlated the decreased mitochondrial population with the sporadic AD [22, 31, 32], besides the perspective that the accumulation of amyloid beta (Aβ) could also be an etiology of mitochondrial lesions [33–35]. In the latest Alzheimer's disease diagnostic models, the assessment of mitochondrial functionality is one of the most crucial factors under investigation [7–21, 36–46]. In the present minireview, we will discuss the role of mitochondrial function in neurodegenerative diseases and highlight the importance of GTPases proteins in mitochondrial dynamics as a mechanism altered during a degenerative event (Fig. 1).

Mitochondrial Population and Mitochondrial Dynamics

The total number of mitochondria inside a cell undergoes continuous cycles of fission and fusion, and each cycle of fusion requires harmonized fusion of inner and outer mitochondrial membranes [47, 48]. Moreover, fusion events have been reported to protect mitochondrial function by allowing them to mix their internal contents, hence facilitating protein complementation, equal metabolite distribution, autophagy promotion, mtDNA repair, and isolation of damaged mitochondrial segments [33, 49]. On the other hand, fission events enhance mitochondrial distribution along cytoskeletal tracks and facilitate the equal division of mitochondria into their daughter cells [33]. These remodeling processes are mediated by distinct protein complexes [47]. Three mitochondrial enzymes responsible for hydrolyzing GTPases are vital for the mitochondrial fusion [47]. The mfn1 and mfn2 GTPases are recruited to the outer mitochondrial membrane and facilitate inter-mitochondrial attachment during the process of fusion. The third GTPase OPA1 is positioned in the transmembrane area and has been reported to facilitate the fusion of inner membranes. Another GTPase the dlp1 is required for the mitochondrial fission events [31, 33, 47] and has been reported to be transported from the cytoplasm, recruited to mitochondrial surface, and utilize GTP hydrolysis to accumulate into large oligomeric complexes to form the tubular network of mitochondria [31]. Citing the significant functions related to mitochondria, it has become easier to visualize fission/fusion–induced morphological changes [34, 47, 48]. Fission events have been reported to create shorter and large number of mitochondria, and hence, mutation in genes required for mitochondrial fission events results in interconnected and excessively elongated mitochondria. Earlier studies have suggested that mitochondrial fission precedes apoptosis [50]. Hence, it seems that fission-mediated mitochondrial fragmentation facilitates the release of mitochondrial proteins thus triggering apoptosis. On the other hand, fission events have been reported to create longer and fewer number of mitochondria, and hence, mutation in genes required for mitochondrial fusion results in fragmented mitochondria [31, 47]. For example, significantly reduced fusion events and inability to survive beyond mid-gestation period have been reported in mice with mutations in opa1, mfn1, mfn2 genes [33]. Moreover, cells devoid of mitochondrial fusion have been reported to show impaired respiration and show heterogeneous properties, thus emphasizing the importance of fusion events for sustaining a healthy and homogenous mitochondrial population [47]. Fusion events have also been reported to cause mixing of mitochondrial genomes, and since the diseases caused due to genomic mutations follow a route reliant on pathogenic mitochondrial DNA segregation, therefore fusion events might have a crucial impact on the outcome of associated diseases.

Several studies present fusion events as processes of considerable physiological importance [47] and defects in mitochondrial fusion as a possible cause of various neurodegenerative disorders [31, 33]. For example, mutations in mfn2 protein cause CMT2A [47], while mutations in the protein opa1 cause DOA [51]. The presence of abundant mitochondria is an ultrastructural feature of a synapse to maintain the levels of ATP production and calcium homeostasis, and the maintenance of healthy nerve transmission is a critical factor. The proper distribution of active mitochondria to axon terminals and dendrites is attributed to the tightly regulated mitochondrial dynamics [52], which in turn is due to the presence of exceptionally long cellular processes of neurons [47]. Decreased mitochondrial motility has been reported due to defects in fission or fusion [48]. For example, in fusion-deficient cells, the large mix of interconnected mitochondria prohibits efficient mitochondrial motility in small pathways like neuronal processes [53]. The cause of this decreased mitochondrial motility in fusion-deficient cells is, however, not very clear [48]. Citing the remarkable role of mitochondrial dynamics in various physiological processes is

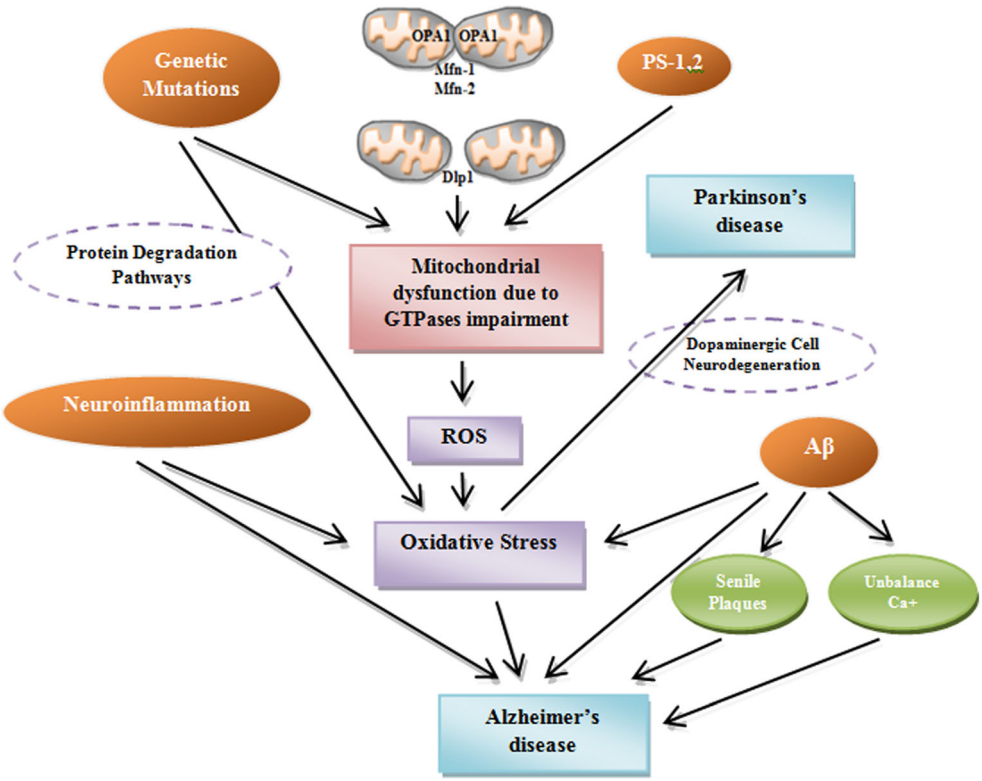

Fig. 1 GTPases and related factors affecting mitochondrial dysfunctions associated with Alzheimer's disease and Parkinson's disease

well expected to find some other diseases caused due to a mutation in the genes controlling mitochondrial fission and fusion [47]. Instead of normal hovering in Brownian motion, fusion-deficient mitochondria lose their directed movement [54]. In mitochondrial fusion-deficient neurons, increased mitochondrial diameter due to aggregation and swelling of mitochondria has been suggested to block an efficient entry into neuritis thus facilitating mitochondrial death in axons and dendrites, and gradually resulting in neurodegeneration [55]. The process of autophagy characterized by self-mediated degradation of cytoplasm and organelles of eukaryotic cells, and works as a non-fatal stress response mechanism by protein recycling for the protection of cells from nutrient deficiency and programmed cell death (PCD) [56]. This mechanism of autophagy is thus also called type II PCD and has been reported in many pathological and developmental conditions [57]. The accumulation of lysosome-originated autophagic vacuoles is another characteristic feature of autophagy, which induces the degradation of various organelles and proteins [31]. There are also some mitochondrial-associated cell death proteins, which may be responsible for aiding in mitophagy [58].

The transport of mitochondria in mammalian cells is based mainly on the microtubules [59]. The interaction of mitochondria with the kinesin-1 motor (KHC, Kif5b) through outer membrane proteins drives the intergraded motion of mitochondria [60]. Having discussed the mitochondrial dynamics entailing fission, fusion, motility, transport, and mitophagy in details [4, 27, 28, 61–66], the process of the coordination of fusion events of inner and outer mitochondrial membranes needs to be understood [67]. A vital clue comes from the observation that mitochondria possess double-membrane architecture thus pointing towards the merging of four membranes into two [67]. The tight fusion of inner and outer mitochondrial membranes has also been indicated by in vivo studies of time-lapse imaging [67]. However, in vitro manipulation of mitochondrial fusion events has suggested mechanistic differences in the fusion of outer and inner mitochondrial membrane [68]. Only outer mitochondrial membranes fuse under limited in vivo GTP concentrations, and a proper regeneration of GTP production system permits the fusion of inner mitochondrial membranes [68]. Likewise, the fusion of inner membranes can be distinguished from the fusion of outer membranes in mammalian cells, and inner mitochondrial membrane fusion has been reported to be specifically blocked by the dissipation of mitochondrial membrane potential [69–71]. Also, mitochondria are sites for the production of ROS (·OH and O_2−) and RNS (NO) [51]. Mitochondria have also been reported to produce endogenous ROS as side products of oxidative phosphorylation [72, 73].

Mitochondria in Alzheimer's Disease

With more than 10,000,000 in Europe and 35,000,000 worldwide, AD is among the six most deadly diseases. Alzheimer's disease is a progressive disorder that leads to dementia and

affects approximately 10% of the population older than 65 years of age [74]. Unfortunately, the AD fear is heavily preserved in our days due to the failed clinical trials for new effective drugs based to the amyloid hypothesis [75]. Recent studies have shown that the first pathophysiological lesions of the disease could start in young ages as well, creating ambiguity for the proper time to administer inhibitory therapy. Medications targeting dementia or depression or advanced nanotechnological products could reduce the cognitive decline or the neuropsychiatric symptoms in AD, but, unfortunately, they do not offer a holistic treatment. Given the complexity of the disease, many research teams globally are focused to alternative solutions such as the valid diagnosis or even prediction [38, 76–85].

The reasoning of why molecular mechanisms cause neurodegeneration in the AD is not known; however, accumulating evidence suggests that beta-amyloid peptide contributes to this degeneration. Previous works [48, 86] suggested the association between amyloid-β (Aβ) toxicity, mitochondrial dysfunction, oxidative stress, and neuronal damage in the AD pathophysiology [87]. The loss of memory corresponds to the first indication of cognitive and behavioral impairments [31]. In the majority of AD cases, these symptoms are correlated to the appearance of senile plaques and neurofibrillary tangles composed by Aβ and hyperphosphorylated tau proteins [22]. Recent evidence has indicated that Aβ can be produced and interacts at the mitochondrial level suggesting a direct mechanism through which this peptide can impact on mitochondrial function [88]. Additionally, a γ-secretase complex composed by nicastrin was identified in mitochondria of rat's brain, generating Aβ intracellular domain [47]. Interestingly, it was shown that Aβ itself could be targeted to the mitochondria by a sequence-like targeting sequence downstream of its endoplasmic reticulum signal sequence [47]. While Aβ mitochondrial targeting is closely related to mitochondrial dysfunction, the mitochondrial cascade hypothesis was proposed for the explanation of late-onset sporadic AD [49]. This assumption states that, in the sporadic late-onset AD, mitochondrial dysfunction is the primary event that causes Aβ deposition and synaptic degeneration. The authors utilized in situ hybridization to mitochondrial DNA to find out that neurons showing increased oxidative damage in the AD also possess a striking and significant increase in mitochondrial DNA. In another study, researchers observed a significant decrease in the activities of the tricarboxylic acid cycle enzymatic complex associated to AD cognitive disability [89]. Additionally in the frontal, parietal, and temporal lobes and cerebellum of AD brains, researchers identified multiple oxidized bases in nuclear and mitochondrial DNA, indicating higher levels of oxidative stress [59]. Altogether, these results suggest that oxidative damage to mitochondrial DNA may contribute to the AD. In addition, in a similar study, a cytosolic accumulation of the α-chain of the ATP synthase at the early stages of neurofibrillary degeneration process was observed [90]. It is specifically observed in degenerating neurons, either alone or tightly associated with aggregates of tau proteins, suggesting a potential new molecular event related to neurodegeneration. Mitochondrial population extracted from AD patients' skin fibroblasts has been reported with significantly less Ca^{2+} in comparison to age-matched controls [91]. Comparison of changes in calcium signaling, mitochondrial oxidation, and Aβ production in fibroblasts from patients with primary genetic defects in the presenilins indicates that changes in signal transduction, calcium included, may be a more stable observation than altered Aβ production in fibroblasts [51, 92]. It is also observed that genes related to mitochondrial energy metabolism and apoptosis are upregulated before and during the appearance of Aβ plaques [93, 94]. Therefore, electrophysiological mitochondrial impairment could lead to an upregulation of mitochondrial genes as a compensatory response [55]. Once more, these Aβ plagues transgenic mice exhibit no plaques but an increase in Aβ levels, reinforcing the notion of a major role of intraneuronal Aβ in inducing mitochondrial dysfunction. It was observed that the addition of Aβ to isolated mouse brain mitochondria could lead to cytochrome c release and mitochondrial swelling [95]. All these cases above indicate a tight correlation between mitochondrial function, Aβ, and neurodegeneration suggesting interdependence among Aβ toxicity and mitochondrial dysfunction [96].

Mitochondria in Other CNS-Related Disorders

The cause of the selective degeneration of nigrostriatal neurons in Parkinson's disease (PD) has remained largely unknown. The progressive dorsoventral dopamine loss causes the classical symptoms of bradykinesia, rigidity, and resting tremor. These symptoms are confronted by replacing current dopamine such as the levodopa strategy. A defect based on the biochemical mechanism of complex I of the mitochondrial respiratory chain has been described in a relatively large group of confirmed PD cases from recent cybrid studies. This indicates that it has a genetic cause and that it may arise from mutations in the mitochondrial DNA. Complex I defects have oxidative stress as an outcome, and thus, they increase the damage of neurons by excitotoxic death. In this way, environmental factors and dysfunction in a mitochondrial level may interact and result in neurodegeneration [7, 97–105]. The mitochondrial mutations involved in PD pathogenesis are supported by sequence analysis of the mitochondrial genome. However, even if mitochondria play a role in cell death, their exact involvement in PD has remained unsolved. This is because classical apoptosis does not appear to function actively in the degeneration of the parkinsonian nigra. While the cause of nigra cell death in PD is still unknown, 1-methyl-4-phenyl-

Table 1 Common neurodegenerative diseases and the related targeted brain regions that is associated with the mitochondrial dysfunction

Neurodegenerative diseases	Brain region
Alzheimer's disease	Cerebral cortex and hippocampus
Parkinson's disease	Substantia nigra
Autism spectrum disorder	Anterior cingulate gyrus, Motor cortex and thalamus
Charcot-Marie-Tooth Type 2A	Peripheral nerves
Transmissible spongiform encephalopathies, multiple sclerosis, spinocerebellar ataxia	Cerebellum
Huntington's disease	Striatum
Dominant optic atrophy	Optic nerve

1,2,3,6-tetrahydropyridine (MPTP)-induced experimental parkinsonism has made a break-through for the investigation of PD. It has been well accepted that the most likely mechanism of nigra cell death is the energy crisis due to mitochondrial respiratory failure [106]. In experimental PD models, dopaminergic neurodegeneration appears to occur, at least in part, through activation of mitochondria-dependent pathways. Researchers performed animal testing with synthetic heroin analog contaminated with the name MPTP. They showed that MPTP in monkey had similar activity with most of the pathological PD symptoms, in mice dopaminergic neurons suffered from degeneration, and in rats, this toxin was resistant [50, 53, 54, 56]. The most profound evidence for a mitochondrial etiology of PD, however, derives from the study of gene disease [57, 58]. Mutations in pink1, which encodes a serine-threonine kinase found in mitochondria, and parkin, which encodes a RING finger-containing E3 ubiquitin ligase, have been found in PD cases [60, 107, 108]. Previously, reports have stated that Drosophila pink1 and parkin function in the same genetic pathway to regulate mitochondrial integrity in testes, muscle, and dopaminergic neurons [109–111]. Careful studies of pink1 and parkin mutant phenotypes in testes suggest the possibility that pink1 and parkin might regulate mitochondrial dynamics, fission, and fusion. The dynamic regulation of mitochondrial morphology is critical to mitochondrial function, where a transition leads to disease [112]. Additionally, while autism spectrum disorder (ASD) is a neurodevelopmental disorder with impaired social interaction, verbal and non-verbal communication, and repetitive behavior, the loss of neurological function can be explained as neurodegeneration, including neuronal cell loss, activated microglia and astrocytes, proinflammatory cytokines, oxidative stress, and elevated 8-oxo-guanosine levels. The existent evidence shows that neurodegeneration underlies the loss of neurological function in children with ASD who have experienced regression and loss of previously acquired skills. It has been found that individuals with ASD have experienced a loss of neuron cells and pyramidal cells in their amygdala. Furthermore, the role of microglia, namely non-neuron cells that are responsible for maintaining homeostasis in the body and for the development of other neurological disorders, may also play a role in neurodegeneration in ASD individuals. Studies have already presented that this microglia can experience neuronal dissolution and can also lead to neurodegeneration by producing toxic cytokines that can damage neurons [67, 68]. In these cases, many regions of the brain with activated microglia were found to be inflamed, and that supports the hypothesis that microglia activation could be evidence of degeneration in ASD. Some findings have suggested that mitochondrial dysfunction and changes in energy metabolism may affect the social and cognitive deficits in ASD [67, 68]. A school-based study of 69 children with confirmed autism found mitochondrial respiratory chain dysfunction in 7.2% [70]. Mitochondrial diseases are more evident in tissues such as available cells from lymphocytes. Findings tested the hypothesis that children with autism have dysfunctional mitochondria in peripheral blood lymphocytes, and researchers observed that there is bioenergetics evidence of progressive, age-related degeneration in the brains of individuals diagnosed with an ASD [69, 71].

Conclusions

When Alois Alzheimer described for the first time AD, it was initially classified as a dementia disorder. Based on recent developments in mitochondrial research, as described above, increased pharmacological and pharmaceutical efforts have to lead to the emergence of mitochondrial medicine as a whole new field of biomedical research. Understanding the role of mitochondrial abnormalities in the pathogenesis of AD opens a window for the design of new therapeutic strategies. There is nowadays evidence that suggests this direct correlation of mitochondria with aging-related neurodegenerative diseases. They are a vital feature of neurodegeneration as they regulate cell death and a risk factor for aging when early mutations occur leading to the mitochondrial DNA and increased oxidative stress. Moreover, a substantial number of specific proteins related to diseases interact with mitochondria [9]. Thus, energy metabolism, free-radical generation, or specific interactions of

proteins related to diseases where mitochondria play a role hold great promise for researchers utilizing therapies targeting basic mitochondrial processes (Table 1).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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