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REVIEW PAPER

# ROS as Regulators of Mitochondrial Dynamics in Neurons

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**Abstract**
Mitochondrial dynamics is a complex process, which involves the fission and fusion of mitochondrial outer and inner membranes. These processes organize the mitochondrial size and morphology, as well as their localization throughout the cells. In the last two decades, it has become a spotlight due to their importance in the pathophysiological processes, particularly in neurological diseases. It is known that Drp1, mitofusin 1 and 2, and Opa1 constitute the core of proteins that coordinate this intricate and dynamic process. Likewise, changes in the levels of reactive oxygen species (ROS) lead to modifications in the expression and/or activity of the proteins implicated in the mitochondrial dynamics, suggesting an involvement of these molecules in the process. In this review, we discuss the role of ROS in the regulation of fusion/fission in the nervous system, as well as the involvement of mitochondrial dynamics proteins in neurodegenerative diseases.

**Keywords** Mitochondrial dynamics · ROS · Neurons · Cell death · Neurodegenerative diseases

## Introduction

Mitochondria have been characterized as the metabolic center of the cell. These organelles contain their own genome (Frezza 2017) and synthesize most of the cellular ATP, nucleotides, fatty acids, and iron-sulfur clusters (Lackner 2014). Additionally, mitochondria play a role in calcium and redox signaling during apoptosis (Galluzzi et al. 2014). Thus, mitochondria have been pointed out as central organelles in cellular function. In the last years, the morphology and structure of these organelles have been shown to be relevant for the physiology of the cell and are indicators of the cellular fate.

Mitochondrial networks are constantly undergoing remodeling via cycles of fission and fusion (Westernmann 2012). In different models, the core of proteins involved in the regulation of the mitochondrial morphology undergo changes of activity and/or expression level by a variety of intracellular signals and metabolic conditions (Wappler et al. 2013; Manczak et al. 2016; Twig et al. 2008). In this review, we discuss some evidences related to the mitochondrial dynamics, including the main components that participate in this process, and its role in some pathophysiological processes, with specific emphasis in the nervous system. Particularly, we discuss the importance of reactive oxygen species (ROS) as mediators of mitochondrial dynamics in neurons and the role of proteins involved in the mitochondrial fission/fusion in neurodegenerative diseases.

## Mitochondrial Dynamics

Mitochondria are continuously dividing and fusing to control their size, morphology, and number. They may exist as individual organelles or as interconnected networks. These different forms of organization and structure depend on the tissue and cell type, as well as the metabolic state and developmental stages of the cell. Mitochondrial morphology is achieved by the constant cristae remodeling, as well as the fission and fusion of the mitochondrial membranes. Altogether, these processes are known as mitochondrial dynamics (Pernas and Scorrano 2016). The maintenance of the mitochondrial organization, as well as their function and morphology is a complex issue orchestrated by a

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heterogeneous group of proteins that keep the equilibrium between form and function by coordinating their activities (Lee and Yoon 2016). The main mechanism of mitochondrial dynamics relies on proteolytic processing and post-translational modifications of the core of proteins involved in the process (Cho et al. 2012).

Mitochondrial fission participates in the control of the number and distribution of mitochondria, as well as in the response to changes in energetic cellular needs, the disposal of damaged mitochondria and the maintaining of the components of the respiratory chain, the cristae shape and the ATP production. On the other hand, fusion is an intricate process that involves the join of outer and inner mitochondrial membrane as an adaptation to facilitate communication between mitochondria and their host cells to maintain cell homeostasis (Pernas and Scorrano 2016). Fusion has been related to the preservation of the capacity of the mitochondria to maintain genetic and biochemical homogeneity, allowing the dissipation of ROS, the exchange of mutated DNA, and the repolarization of membranes to maintain mitochondrial functionality. Fission and fusion determines the structural and functional status of mitochondria (Santel and Frank 2008; Balog et al. 2016).

## Fusion and Fission Machinery

Mitochondrial dynamics is highly regulated by at least four conserved dynamin-related GTPases that mediate the membrane remodeling through the join or scission of mitochondrial membranes (Westermann 2010). The most studied proteins are dynamin-related protein 1 (Drp1), which controls mitochondrial division, as well as mitofusins 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (Opa1), which drive fusion. The general mechanism and main components are discussed below and are shown in Fig. 1.

The key protein involved in mitochondrial scission is the soluble Dynamin-Related Protein (DRP1, in humans), which controls division of the mitochondrial outer membrane (Ingerman et al. 2005; Mears et al. 2011; Nakamura et al. 2006; Karbowski et al. 2007; Chang and Blackstone 2007a, b; Cho et al. 2009; Chang et al. 2010). Their role in fission is conserved in all the characterized eukaryotes to date, including plants, and it is ubiquitously expressed in mammals. It is encoded by the DNM1L gene and its known as dynamin-1 (Dnm1) in yeast and there are other homologs in different species (Labrousse et al. 1999; Bleazard et al. 1999, 2013). It is noteworthy to note that Drp1 and some of its partners also mediate fission of peroxisomes (Bertholet et al. 2016). Drp1 undergoes post-translational modifications, which can affect its activity and cellular localization; the main modifications include S-nitrosylation (Nakamura et al. 2006; Karbowski et al. 2007; Chang and Blackstone

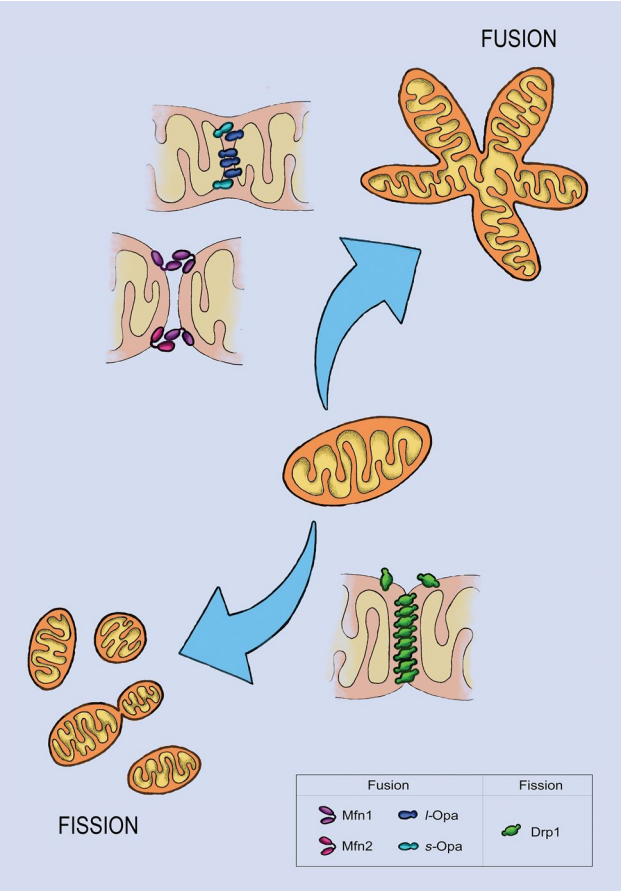


**Fig. 1** Schematic representation of main components of mitochondrial dynamics machinery. Mitochondrial morphology is dependent on a proper balance between fusion and fission processes, which are coordinated by a systematized set of dynamin-related GTPases. Fusion of mitochondrial outer membrane is leading by Mfn1, Mfn2, which are anchored in the outer membranes and allows their close up and the fusion of membranes. Opa1 is in charge of the connection of the inner mitochondrial membrane and the cristae remodeling. Fusion of mitochondrial membranes produces an interconnected organelle. On the other hand, Drp1 is the master protein for mitochondrial fission and is initially positioned at the outer mitochondrial membranes by adaptor proteins. It leads membranes scission by forming a ring around the organelle to constrain the membranes producing mitochondrial shortening

2007a, b; Cho et al. 2009; Chang et al. 2010), phosphorylation (Taguchi et al. 2007; Han et al. 2008; Sesaki et al. 2014; Manczak et al. 2012), and sumoylation (Prudent et al. 2015).

During the fusion process, several proteins participate as mediators in the remodeling of outer and inner membranes. These include GTPases, Mfn1, Mfn2, and Opa1, among others. Mitofusins are known as Fzo (Fuzzy onions) in flies and yeast, as wells as Mfn1 and Mfn2 in humans (Mozdy and Shaw 2003). Regarding the structure, Mfn1 and Mfn2 share N-terminal regions, where the GTPase domains responsible for the binding and hydrolysis of GTP are located. (Huang et al. 2011; Palmer et al. 2011; Santel et al. 2003). The main

post-translational modifications reported for mitofusins are phosphorylation for the regulation of the mitochondrial fusion and ubiquitination to facilitate mitophagy, i.e., the mitochondria elimination by autophagy (Leboucher et al. 2012; Gegg et al. 2010; Park et al. 2009).

Opa1 is located at the inner mitochondrial membrane. Its biological relevance was established in a homozygous mouse model, which die in utero during embryogenesis. Heterozygous animals are viable, but exhibit loss of retinal ganglion cells and eventually a severe degeneration in nerve fiber layer (Alavi et al. 2007). Opa1 is synthesized in the cytoplasm and is processed in the mitochondrial matrix (Ishihara et al. 2006). It has eight different isoforms in humans and is enriched in retina, brain, testis, heart, and muscle (Delettre et al. 2001). Post-translational regulation is based on the proteolytic processing by mitochondrial metalloproteases that generate a long form that retain the N-terminal transmembrane domain (L-Opa1) and a short soluble isoform (S-Opa1) (Song et al. 2007; Ehses et al. 2009; Anand et al. 2014). Opa1 regulates the shape and the length of the mitochondrial cristae during apoptosis through the participation of oligomers of L-Opa and S-Opa (Frezza et al. 2006).

## Physiological and Pathological Role of Mitochondrial Dynamics

In the physiological context, mitochondrial dynamics is particularly crucial for the regulation of the number of mitochondria, the elimination of organelles by mitophagy (Wu et al. 2018). It is also necessary for the distribution of mitochondria along the cells, since mitochondria are required to be accumulated in sites where high amount of energy or calcium buffering are needed (Otera and Mihara 2011). The importance of mitochondrial fission/fusion has been shown in different physiological processes including apoptosis, cell division, metabolism, and bioenergetics (Westermann 2010; Kanfer et al. 2017; Otera and Mihara 2011; Gomes et al. 2011; Chen et al. 2003; Amchenkova et al. 1988).

Recent studies have shown that aberrations in mitochondrial dynamics processes are associated with many human disorders (Huang et al. 2013; Itoh et al. 2013; Reddy 2011; Reddy and Shirendeb 2012; Cho et al. 2010; Knott et al. 2008). It is known that the loss of mitochondrial function, secondary to defects in mitochondrial dynamics, leads to an increase of ROS generation and a decrease in the ATP production (Guo et al. 2015).

Some human hereditary diseases are linked to defects in the activity of fusion and fission proteins. For example, it has been observed an inadequate function of Drp1 involved in a development delay, insensitivity to pain and microcephaly, as well as in syndromes such as sudden death (Waterham et al. 2007). Some types of lung cancer (Zhu et al. 2004; Chiang et al. 2009) have also been related to an altered function of Drp1, while spastic paraplegia syndrome and multiple sclerosis are associated with defects in Opa1 (Chao de la Barca et al. 2016). Similarly, recent evidence suggests the participation of mitochondrial dynamics proteins in acquired diseases. For example, alterations in mitofusins have been linked to diabetes mellitus, pulmonary hypertension, and breast cancer (Yu et al. 2009; Zhao et al. 2013; Sharp et al. 2014; Ryan et al. 2013) and Opa1 defects are observed in patients with hypertension (Jin et al. 2011).

## Mitochondrial Dynamics in the Nervous System

Due to their high metabolic activity, neurons are particularly sensitive to changes in the mitochondrial function and are energetically demanding cells that require an adaptively maintenance of these organelles (Kann and Kovacs 2007). Moreover, as highly polarized cells containing complex neuritic processes, neurons also need a timely and appropriate transport and distribution of mitochondria to produce energy and regulate the calcium necessary for the neuronal activities, including synaptic transmission and vesicle recycling (Sheng and Cai 2012). Mitochondrial dynamics has also been related to neurogenesis during neuronal development and adult brain. Although the influence of the mitochondrial dynamics in this process has not been completely understood, it is evident that it results an important regulatory event for neuronal development (Khacho and Slack 2018).

The numerous structural profiles of mitochondria correlate with the different bioenergetics demands in several tissues, including the brain. Neurons depend on oxidative phosphorylation as primary source of energy production, which is vital to regulate complex dynamics that include the activity of pumps and transporters, the transport for long distances across neuritic extensions, as well as other processes such as fission and fusion that imply large ATP needs (Kuznetsov et al. 2009; Mironov 2009; Rolfe and Brown 1997).

In neurons, mitochondrial division is important to transport mitochondria to sites where high amount of energy is required, including synaptic terminals (Otera and Mihara 2011). Distribution of these organelles is particularly important in neurons due to the need to delivery and exchange of newly mitochondria along the processes. Thus, the biogenesis is crucial for the availability of healthy mitochondria (Schwarz 2013). Deficiencies in the mitochondrial dynamics are associated with the inability of neurons to maintain the ATP synthesis required for calcium regulation, neuronal electrical activity and axonal transport necessary for neuronal communication (Cuesta et al. 2002; Chen et al. 2003;

Wakabayashi et al. 2009; Shields et al. 2015; Dietrich et al. 2013).

During physiological conditions, it has been demonstrated that mitochondrial length is critical to define when a mitochondria should divide, but the motility is also determinant for fusion. This suggests that the equilibrium of the mitochondrial dynamics is finely regulated not only by a core of proteins, but also for other processes that affect the number and movement of mitochondria, which in turn exerts a feedback to control mitochondrial homeostasis in neurons (Cagalinec et al. 2013). In stress conditions, the length and shape of mitochondria usually adapting their shape form filamentous to short and round, showing the adaptability of these organelles for contend with the changing environment (Youle and van der Bliek 2012).

## Nervous System Pathologies Associated with Mitochondrial Dynamics Defects

Despite the fact that different neuronal populations are affected in neurodegenerative diseases, a common condition in all cases is an abnormal mitochondrial structure and function. This suggests that the mitochondrial dynamics might not be involved in the selective vulnerability of specific neuronal populations, but rather in the mediation or amplification of mitochondrial dysfunction and neuronal death during the course of neurodegenerative or neuropsychiatric disorders (Jellinger 2009; Rezin et al. 2009). The pathologies associated with defects in fission and fusion proteins includes status epilepticus and schizophrenia in which activation of Drp1 is frequently reported (Flippo and Strack 2017; Kim and Kang 2017).

In several neurodegenerative diseases and disorders related to mitochondrial defects, the neurons show alterations in the oxidative phosphorylation, the homeostasis of intracellular ROS and the levels of calcium, as well as in the mitochondrial mobility, mitophagy and fusion/fission dynamics (Burte et al. 2015; Ryan et al. 2015). Deregulation of the mitochondrial fusion or fission has also been associated with defects in neuronal development and neuronal plasticity, both in ex vivo and in vivo models (Bertholet et al. 2016). In Drp1 mutant cultured neurons, abnormal mitochondrial distribution results in a compromised synapse formation. It is also known that lacking of Drp1 causes developmental abnormalities in mice, which die after embryonic day 12.5; these mutant embryos have a small body size and a heart and liver abnormal development (Ishihara et al. 2009).

Neuropathologies such as Alzheimer's, Parkinson's, and Huntington's diseases are characterized by a progressive loss of neuronal function and have been related to mitochondrial defects as an early sign of neurodegeneration (Gao et al. 2017; Correia et al. 2012; Itoh et al. 2013; Wilson et al. 2013). For example, in genetic models of Parkinson's disease, an overexpression of mutant α-synuclein leads to defects on axonal mitochondrial transport and an elevated mitochondrial fragmentation (Devoto et al. 2017; Ordonez et al. 2017), suggesting a close correlation between α-synuclein an mitochondrial distribution in this disease.

In postnatal mouse cortical neurons, apoptotic conditions decreased the expression of Drp1 and parkin and these effects were abolished by recovering the expression levels of parkin or Drp1, which enhanced neuronal viability and reestablished the mitochondrial morphology (Wang et al. 2013). It is known that mutations in the genes that codify for parkin are the cause of the autosomal recessive form of Parkinson's disease. Parkin recognizes proteins of the mitochondria in response to cellular insults and promotes the repair of mitochondria though autophagy and proteasomal mechanisms (Seirafi et al. 2015).

There are evidences suggesting that Drp1 and parkin work in a synergistic manner to maintain mitochondrial function and structure in the brain. Both molecules are critical when mitochondrial division is altered, which suggests that the initiation and progression of Parkinson's disease are related to a decrease in the mitochondrial division and depend on these molecules (Kageyama et al. 2015). The machinery that links Drp1 to the origin and evolution of Parkinson's disease is unclear; nevertheless, it has been demonstrated that Drp1 is closely modulated by different conditions that are also involved in Parkinson's disease. For example, Drp1 levels are quite sensitive to induction of autophagy. In cultured striatal neurons, mitochondrial fission and Drp1 levels are decreased after autophagy induction and the inhibition of autophagy induces high level of Drp1. Thus, It is possible that the observed fission in neurodegeneration could be counteracted by autophagy through a reduction in Drp1 (Purnell and Fox 2013).

Other conditions affecting Drp1 and parking modulation may also play a pivotal role in Parkinson's disease. This includes Drp1 and parkin sumoylation that interferes with mitochondrial fusion/fission by reducing the amount of parkin available for mitochondrial recruitment (Guerra de Souza et al. 2016). Finally, in a model of Parkinson's disease, it was shown that the S-nitrosylation of parkin leads to an increase in the levels of Drp1, but a reduction in its interaction with Drp1. This condition also induces the phosphorylation of Drp1 Ser616 and its recruitment to the mitochondria (Zhang et al. 2016).

Drp1 defects have also been observed in cells of Alzheimer's disease patients (Song et al. 2011; Kandimalla and Reddy 2016). In Alzheimer's disease, fibroblast and human neuroblastoma SH5YSY cells, both the expression of Drp1, and its interaction with mitochondrial adaptors are markedly increased by Aβ-42 (Kuruva et al. 2017). In contrast, the inhibition of Drp1 interaction with its adaptors reduces the

recruitment of Drp1 and prevents the mitochondrial fission and functional dysfunction induced by Aβ-42 (Joshi et al. 2017). On the other hand, in cultured cortical neurons, the amyloid peptide Aβ- 42 increases the expression of Drp1 and decreases the expression of Mfn1/2 and OPA- 1; the inhibition of DRP1 markedly reverts the observed disruption of mitochondrial membrane potential (Han et al. 2017).

Opa1 was identified as the human gene of autosomal dominant optic atrophy (ADOA) that is a hereditary optic neuropathy that causes progressive loss of vision (Delettre et al. 2000). Although initially Opa1 localization and function were unknown, it was later found a signal peptide sequence for mitochondrial localization, suggesting a mitochondrial function of this protein (Alexander et al. 2000). Mutations in Opa1 are responsible of a spectrum of diseases such as ADOA with deafness and multi-systemic syndromes, which involves neurological and neuromuscular symptoms (Amati-Bonneau et al. 2009). Additionally, there are evidences of abnormal cristae morphology in the striatum and cortex of murine models of Huntington's disease due to Opa1 defective oligomerization (Hering et al. 2017).

Regarding mitofusins, it has been known that mutations in Mfn2 are the most common cause of axonal Charcot-Marie-Tooth disease (CMT) type 2 (Züchner et al. 2004), which is a genetically heterogeneous disorder of peripheral neuropathies, characterized by distal muscle weakness and atrophy (Azzedine et al. 2012). In addition, in a model for idiopathic PD induced by paraquat, the observed mitochondrial fragmentation and dopaminergic neurodegeneration are markedly reduced by overexpression of Mfn2 (Zhao et al. 2017). In contrast to Mfn2, there are no reports showing a relation of Mfn1 to any neuropathology.

Neurons are particularly sensitive to alterations in mitochondrial dynamics, which seems to be important in the initiation and progression of neurodegenerative disorders; unfortunately, no much information exists about the mechanisms involving mitochondrial dynamics and the development of neuropsychiatric disorders. The mitochondrial fusion/fission represents a new scenario to explore the pathologies associated to nervous system, but more studies are needed to understand the complete role on these pathologies and their probable therapeutic approach. Some neuropathologies related to defects on mitochondrial dynamics and the role of fission and fusion in these processes are listed in Table 1.

## Regulators of Mitochondrial Dynamics

Despite the experimental evidences about the post-translational regulation of mitochondrial dynamics proteins, the molecular mechanism is still not fully understood. In that regard, it is known that some signaling molecules influence the fusion and fission processes. Two conditions that seem to be mediators of fission and fusion in the nervous system include the intracellular levels of calcium and ROS levels.

Calcium is a ubiquitous cellular messenger involved in signaling pathways that regulate numerous processes. In the nervous system, calcium is critical for several events, including synaptic transmission (Jones and Smith 2016), cell migration (Komuro et al. 2015), and axonal guidance (Kaplan et al. 2014). The role of calcium in mitochondrial dynamics has been extensively reviewed. For example, it has been reported that an increase in the levels of calcium alters both the mitochondrial function and Drp1 activity (Hom et al. 2007). Other studies have demonstrated that the intracellular localization of Drp1 in neurons is regulated by calcium through the participation of calcineurin (Cereghetti et al. 2008; Cribbs and Strack 2007). In addition, under excitotoxic conditions, the levels of Drp1 and Opa1 are mainly affected by a rise in intracellular calcium (Wang et al. 2015; (Martorell-Riera et al. 2014; Jahani-Asl et al. 2011).

In addition to calcium, ROS are also important for the remodeling of mitochondrial architecture, probably by acting on some of the proteins responsible for the mitochondrial dynamics. In contrast to calcium, no much information is available about this topic in the nervous system.

## Reactive Oxygen Species and Mitochondrial Dynamics

ROS are reactive metabolites of oxygen that can be radicals, such as superoxide anion and hydroxyl anion, or no-radicals, including hydrogen peroxide. All of them have a pivotal role in physiological and pathological processes. There are different ROS sources in the cell: xanthine oxidase, lipooxigenase, cyclooxygenase, and NADPH oxidase (NOX), among others (Nayernia et al. 2014, Phaniendra et al. 2015). Mitochondria also generate ROS, mainly as a byproduct of respiration. In all cases, ROS contribute to the redox signaling in the cell (Murphy 2009). Conventionally, mitochondrial complex I (NADH Coenzyme Q Oxidoreductase) and complex III (Ubiquinol-Cytochrome c reductase) are the major contributors of ROS production, but other enzymes in mitochondrial matrix have also been reported as noteworthy ROS producers (Andreyev et al. 2015; Angelova and Abramov 2016).

Experimental evidence shows that the redox signaling is important for the mitochondrial dynamics in several cell types and that the levels of ROS are closely related to the function of the proteins involved in fission or fusion. There is evidence relating the oxidative microenvironment to the modification of these proteins, as well as to the regulation of the mitochondrial dynamics (Mailloux et al. 2013). Thus, alterations in the ROS levels lead to deficiencies in the regulation of mitochondrial morphology and function (Willems

**Table 1** Role of the core of proteins involved in mitochondrial dynamics in neuropathologies

| Protein | Pathology | Action | References | Model |
|---|---|---|---|---|
| Drp1 | Traumatic brain injury (TBI) | ↑ fission | Fischer et al. (2016) | CCI of adult Sprague–Dawley rats |
| | | | Wu et al. (2018) | TBI in adult male ICR mice |
| | Amyotrophic lateral sclerosis (ALS) | ↑ fission | Altanbyek et al. (2016) | Elav-gal4, Mhc-gal4, and D42-gal4 Drosophila line |
| | | | Joshi et al. (2017) | NSC34 cells stably expressing WT or G93A hSOD1 |
| | Huntington's disease (HD) | ↓ fusion | Song et al. (2011) | Neurons and fibroblasts of HD mice |
| | | | Shirendeb et al. (2012) | Mutant Htt expression in generated BACHD mouse |
| | Alzheimer's disease (AD) | ↓ fusion | Kandimalla and Reddy (2016) | Drp1 heterozygote knockout mice and APP mice |
| | | | Kuruva et al. (2017) | AD neurons treated with DDQ |
| | Parkinson's disease (PD) | ↑ Fission | Filichia et al. (2016) | MPTP administration regimen in C57BL/6 mice |
| | | | Ordonez et al. (2017) | Drosophila model of α-synucleinopathy phenotypes |
| Opa1 | Leber's hereditary optic neuropathy (LHON) | ↑ fission | Amati-Bonneau et al. (2009) | Eye-specific homozygous OPA1 Drosophila mutant |
| | Kjer's optic atrophy (KOA) | | Schild et al. (2013) | Patients with heterozygous mutation in the OPA1 |
| | Huntington's disease (HD) | | Hering et al. (2017) | R6/2 transgenic mice (B6CBATg(HDexon1)62Gpb/1 J) |
| | Autosomal dominant optic atrophy (ADOA) | | Delettre et al. (2000) | Patients (ex vivo) exhibited typical signs of DOA |
| | | | Zhang et al. (2017) | Lymphoblastoid cell lines carrying the OPA1 mutation |
| | Autosomal dominant optic atrophy and deafness (ADOAD) | | Liguori et al. (2008) | A family with a unusual phenotype of ADOAD |
| | | | Amati-Bonneau et al. (2009) | Eye-specific homozygous OPA1 mice mutant |
| | Spastic paraplegia (SP) | | Yu-Wai-Man and Chinnery (2011) | Blood 28-yo female with early-onset optic atrophy |
| | | | Pareyson et al. (2015) | Patients with OPA1 mutations in the North of England |
| | Leigh syndrome (LS) | | Rubegni et al. (2017) | Muscle and skin punch biopsies |
| Mnf2 | Alzheimer's disease (AD) | ↓ fusion | Martín-Maestro et al. (2017) | Cell cultures of fibroblast cell lines from SAD |
| | | | Manczak et al. (2018) | Amyloid beta precursor protein mice (Tg2576 mice) |
| | Charcot-Marie-Tooth disease (CMT) | | Azzedine et al. (2012) | Patients with MFN2 mutations and sensorineural hearing loss. |
| | | | Dankwa et al. (2018) | Blood samples of 6 family members - from a large CMT2 family |
| | Parkinson's disease (PD) | | Gautier et al. (2016) | Human fibroblasts obtained from skin biopsies (PD patients) |

et al. 2015). In spite of all this information, in the majority of the cases, the mechanism of this regulation is still unknown.

The mitochondrial fusion in HeLa cells and MEFs depends on the cellular oxidizing conditions. In these cells, oxidized glutathione (GSSH) stimulates this process. Furthermore, cysteine 684 seems to be important for the Mfn2 oligomer formation, since the mutant C684A resulted in a loss of GSSG-mediated oligomers disturbing mitochondrial network (Shutt et al. 2012). It is possible that local ROS production in mitochondria could be responsible for the modulation of the activity and/or expression of mitochondrial dynamic proteins. In other non-neuronal cell lines, it was found that ROMO1 (Reactive Oxygen Species Modulator 1), a mitochondrial key protein involved in the regulation

of ROS and cell death (Lee et al. 2010; Kim et al. 2010a, b), modulates the cristae morphology and the mitochondrial fusion. ROS regulate ROMO1 activity by the control of the redox sensitive cysteines, Cys15 and Cys79. Additionally, ROMO1 is essential for Opa1 oligomerization required for maintaining the integrity of cristae junctions and preventing the leakage of cytochrome C (Norton et al. 2014).

## ROS as Regulators of Mitochondrial Dynamics in Neurons

In neurons, multiple conditions involved in physiological processes, such as proliferation, neurite outgrowth, differentiation, among others, have been related to oxidant conditions (Le Belle et al. 2011; Olguín-Albuerne and Morán 2015; Piras et al. 2016). In this context, ROS production has also been linked to the mitochondrial form and function in neurons. On the other hand, it has been reported abnormal forms of mitochondria in some models of neuropathological diseases, in which ROS production is involved.

The loss in the fusion and fission balance has been related to oxidative stress in neurons (Knott et al. 2008). Fission is probably the most studied event related to ROS production in neuronal models. In general, an elevation of ROS levels triggers mitochondrial fragmentation. This condition also leads to a modification of Drp1 activity. In cerebellar Purkinje cells, the loss of Drp1 causes neuronal damage, probably because mitochondrial division is necessary for their distribution in dendrites during neurite extension. In this regard, antioxidant treatment prevents mitochondrial morphological changes and cell death in KO Drp1 neurons, indicating that ROS production is involved in this process, and showing that mitochondrial fission capacity is important to avoid neurodegeneration (Kageyama et al. 2012).

There is evidence suggesting a connection between Drp1 and ROS (Cho et al. 2012). It has been observed that inducing Drp1 phosphorylation causes mitochondrial fission after 30 min, which also generates neuronal death (Zhou et al. 2017). On the other hand, amyloid β protein (Aβ) causes Drp1 phosphorylation mediated by Akt, which generates excessive mitochondrial fragmentation, elevation of ROS levels and subsequently neuronal apoptosis (Kim et al. 2016). In an Alzheimer's disease model, increased mitochondrial ROS levels lead to a shortening of mitochondria and to an increase in Drp1 activation by Ser616 phosphorylation (Cho et al. 2012).

Recently, it was described that in hippocampal neurons treated with Aβ the mitochondria take a granular shape, which is different to the typical spherical shape reported in the literature after an oxidant stimulus. Besides, the granular shape also depends on ROS, but the expression of mitochondrial dynamics proteins was not affected, suggesting a different mechanism from those described until now (Hung et al. 2018). The different stimuli that induce ROS levels have heterogeneous effects on mitochondrial fragmentation, as well as on the neuronal death process, but it is clear that a correlation exists between ROS increase and Drp1 activation, although the details in the mechanism have not been elucidated.

ROS production seems to exert also an effect on the fusion machinery. Specifically, it has been reported an influence of ROS over Mfn2 and Opa1. In cerebellar granule neurons, potassium deprivation and hydrogen peroxide induce mitochondrial fragmentation; however, under these conditions, the expression of Mfn2 reverts the mitochondrial shortening and prevents neuronal death, showing that Mfn2 overexpression promotes mitochondrial and neuronal viability (Jahani-Asl et al. 2007). In the same model of cerebellar neurons, the increase of ROS levels causes Opa1 cleavage at the N-terminal and the residue K301 is removed, leading to protein deactivation; finally, this condition results in mitochondrial fragmentation and dysfunction, as well as apoptosis, suggesting that mitochondrial fusion imbalance can compromise neuronal viability (Gray et al. 2013).

Interestingly, Opa1 deletion during early in vitro neuronal development also causes ROS increment and NRF2 translocation accompanied by a transitory mitochondrial hyperfilamentation, which correlates with the onset of synaptogenesis. Additionally, the lack of Opa1 induces a decrease of the expression of pre- and post-synaptic proteins and a reduction in the number of synapses (Bertholet et al. 2013). These results suggest that mitochondrial dynamics proteins expression related to ROS production is critical for the neuronal development. Consistently, $Opa1^{+/-}$ neurons are more sensitive to oxidative stress, probably because their antioxidant proteins suffer a reduced expression; these cells also show mitochondrial dysfunction, a decrease of oxygen consumption and cell death (Millet et al. 2016). Therefore, it seems that the defective expression of fusion proteins affects the response of cells against oxidant conditions, making them more susceptible to oxidation and subsequently to cell death.

It is clear from the literature that it is not totally understood the role of ROS in the mitochondrial dynamics and that more studies are needed to establish a relationship between these molecules and the expression and activity of Drp1, Opa1, and mitofusins. The main effect of ROS on the shape and function of neuronal mitochondria is depicted in Fig. 2.

## Conclusions

Mitochondrial fusion and fission balance is critical to contend with the high energetic demand necessary to maintain the physiological cell functions, particularly in neurons.

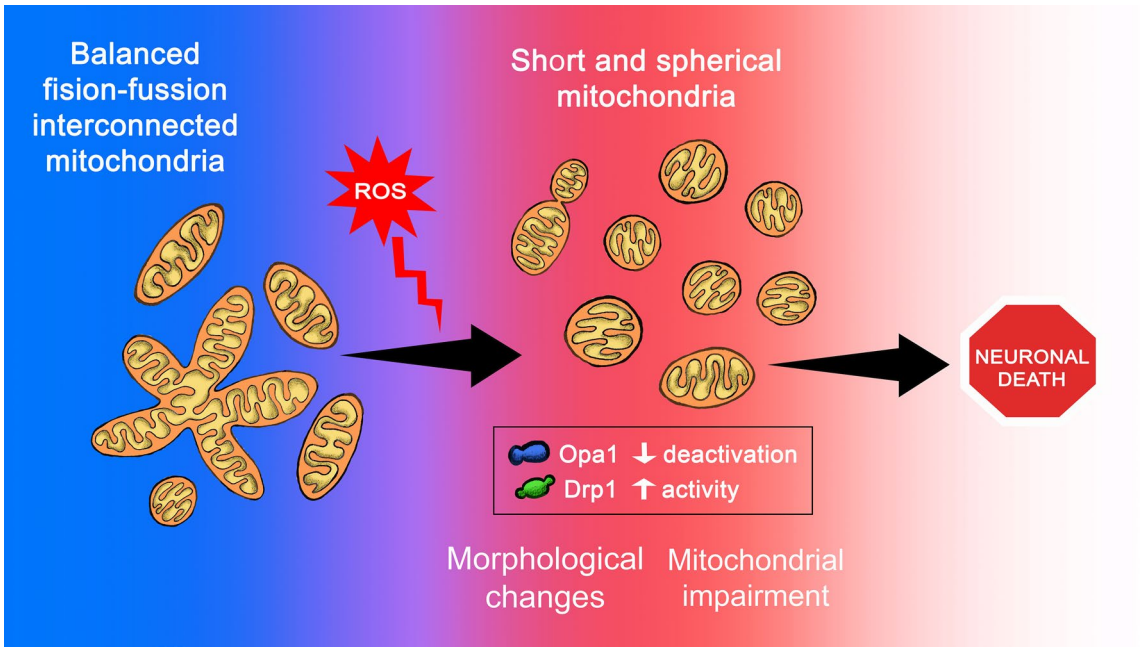


**Fig. 2** Consequence of ROS levels on mitochondrial dynamics in neuronal cells. In neurons, mitochondria require a balance between fission and fusion to maintain cell homeostasis. This balance is lost in elevated ROS environments, which induces Drp1 activation, Opa1 deactivation, and mitochondrial fragmentation, leading eventually to neuronal death. Conversely, the reduction or scavenging of ROS by several conditions induces the elongation of mitochondrial network

In this context, most of the studies have been targeted to elucidate the contribution of the mitochondrial dynamics in some neuropathologies. ROS are important mediators in mitochondrial function and cellular health and have been point out as regulators of mitochondrial dynamics in several physiological and pathological processes. It is known that the loss of balance between fusion and fission is related to an increase of ROS production. This condition leads to a loss of mitochondrial membrane potential, a decoupling of the electron transport chain and the fall of ATP concentrations. The cellular ROS levels influence the expression and activity of Drp1, Opa1, and mitofusins, which in turn modulate the neuronal fate.

## Future Challenges

The role of ROS in the regulation of mitochondrial dynamics is critical for several neurodegenerative disorders. One of the earliest signals in the pathophysiological process of neurodegeneration is an imbalance of ROS. It is therefore important to investigate the temporary course of ROS changes in relation to the proteins involved in fission or fission, as well as in the molecular pathways that are activated in this process. In addition, it would be particularly interesting to explore more exhaustively the action of ROS in the regulation of the mitochondrial dynamics process through redox modifications of specific amino acids. Thus, strategies to modify both the ROS production and abnormal mitochondrial dynamics may be an attractive therapeutic target for the treatment of neurodegenerative diseases. In this context, more studies are needed to understand the mechanisms responsible for the regulation of mitochondrial fission and fusion in pathological conditions. Progress exists in screening, identifying, and developing molecules as target therapies to reduce mitochondrial fission, maintaining mitochondrial fusion and cell survival; however, more information about neuronal physiological roles of mitochondrial dynamics is needed.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare that there is no conflict of interests.

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