

VOLUME 8 ISSUE 2 2022

ISSN 2454-3055



INTERNATIONAL JOURNAL OF ZOOLOGICAL INVESTIGATIONS

***Forum for Biological and
Environmental Sciences***

Published by Saran Publications, India



International Journal of Zoological Investigations

Contents available at Journals Home Page: www.ijzi.net

Editor-in-Chief: Prof. Ajai Kumar Srivastav

Published by: Saran Publications, Gorakhpur, India



ISSN: 2454-3055

Reactive Oxygen Species Effects on Mitochondrial Dynamicity that may Lead to Parkinson's Disease: A Review

Sarkar Diptendu

Department of Microbiology, Ramakrishna Mission Vidyamandira, Belur Math, Howrah 711202, West Bengal, India

Received: 28th June, 2022; **Accepted:** 4th August, 2022; **Published online:** 12th August, 2022

<https://doi.org/10.33745/ijzi.2022.v08i02.030>

Abstract: Parkinson's disease (PD), is the second common and deadliest neuronal and a multisystem disorder that contributes to significant morbidity and healthcare burden in the world. Its causes are poorly understood and there is no proven therapeutic line of attack to foil the disease progression. The neuropathological studies of Parkinson's disease brains show irreversible relapse of dopaminergic neurons in substantia nigra and other brain regions, and a simultaneous loss of dopamine (DA) in the striatum may be one of the main reasons for this disease. But now a days it is known that mitochondria, has a great role to promote so many neurological disorders along with Parkinson's disease. Defects in neuronal development and neuronal plasticity are related with the deregulation of the mitochondrial fusion or fission process. On the other hand result of mitochondrial dis-regulation is, generation of reactive oxygen species (ROS), which also activate some specific pathways that cause ultimately cell damage and finally neurological disorder like PD. In this review it is intended to gather current knowledge about the relation between mitochondria and ROS with PD. It is true that this is playing key role in PD so, targeting all the pathways related to this dysfunction and modification in this field can be helpful to create a new therapy.

Keywords: Parkinson's disease, Reactive oxygen species, Fission, Fusion, Neuron damage

Citation: Sarkar Diptendu: Reactive oxygen species effects on mitochondrial dynamicity that may lead to Parkinson's disease: A review. Intern. J. Zool. Invest. 8(2): 237-244, 2022.

<https://doi.org/10.33745/ijzi.2022.v08i02.030>



This is an Open Access Article licensed under a Creative Commons License: Attribution 4.0 International (CC-BY). It allows unrestricted use of articles in any medium, reproduction and distribution by providing adequate credit to the author (s) and the source of publication.

Introduction

Parkinson's disease (PD), is the second common and deadliest neuronal and a multisystem disorder that contributes to significant morbidity and healthcare burden in the world (Pringsheim *et al.*, 2014). Its causes are poorly understood and there is no proven therapeutic line of attack to foil the disease progression (Onyou Hwang, 2013). Characteristics of this disease include tremor at rest, rigidity, bradykinesia and postural instability. Premotor and non-motor symptoms of

Parkinson's disease include constipation, hyposmia, REM-sleep behaviour disorder, as well as cognitive, neuropsychiatric, autonomic and sensory disturbances (Goldman and Postuma, 2014). Recent neuropathological studies of Parkinson's disease brains show irreversible relapse of dopaminergic neurons (Fig. 1) in substantia nigra and other brain regions, and a simultaneous loss of dopamine (DA) in the striatum may be one of the main reasons for this

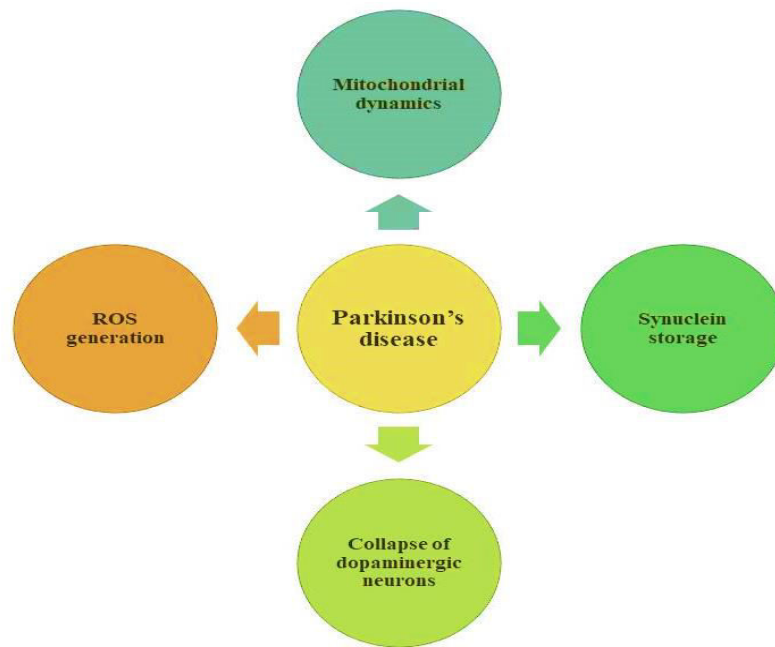


Fig.1: Main cause of Parkinson disease.

disease (Rietdijk *et al.*, 2017).

Aggregation of alpha-synuclein and Lewy bodies are present in the soma of the spared neurons in different cerebral region. At present, the pathogenic implication of these is a birthplace of much debate among researchers but the alpha-synuclein (SNCA) which codes for alpha-Syn, a 140-aa protein, was the first gene in which mutations causing PD (PARK1; or PARK4) were recognized (Carolina *et al.*, 2018). Apart from SNCA, mutations in 15 other proteins are related to autosomal dominant and recessive forms of PD, including LRRK2 (PARK8), PINK1 (PARK6), PARKIN (PARK2), and DJ-1 (PARK7). Mutations in all of these proteins cause for all intents and purposes the AME clinical characters and pathology, proposing that they all participate in a common pathogenetic path. As Lewy bodies holding alpha-Syn are present in most PD patients, so perhaps alpha-Syn plays a role in this common pathway (James Surmeier *et al.*, 2017; Carolina *et al.*, 2018). But the real interesting thing is that mitochondria has a great role in this.

It is well known to us that Mitochondria is the metabolic center of the cell. It has their private genome (Frezza, 2017) and manufactures most of

the cellular ATP, nucleotides, fatty acids, and iron-sulfur collections (Lackner, 2014). Mitochondria are necessary to be mounting up in sites where high amount of energy or calcium buffering are desired in neural activities (Otera and Mihara, 2011). In quite a few neurodegenerative diseases and disorders interrelated to mitochondrial failings, the neurons show modifications in the oxidative phosphorylation, the homeostasis of intracellular ROS and the levels of calcium, as well as in the mitochondrial kinesis, mitophagy and fusion/fission dynamics (Burte *et al.*, 2015; Ryan *et al.*, 2015). Defects in neuronal development and neuronal plasticity related with the deregulation of the mitochondrial fusion or fission has also been associated with both in *ex vivo* and *in vivo* models (Berthol *et al.*, 2016). So it is the concluding point that loss of mitochondrial functionality related with so many neurological disorder, including Parkinson's disease. According to current evidence, Mitochondrial damage, production of ROS, loss of calcium supply, Imbalance between fission and fusion of mitochondria, and mitochondrial fragmentation leading eventually to neuronal death and loss of neuron to neuron communication (Fig. 2). Thus, strategies to adjust abnormal mitochondrial

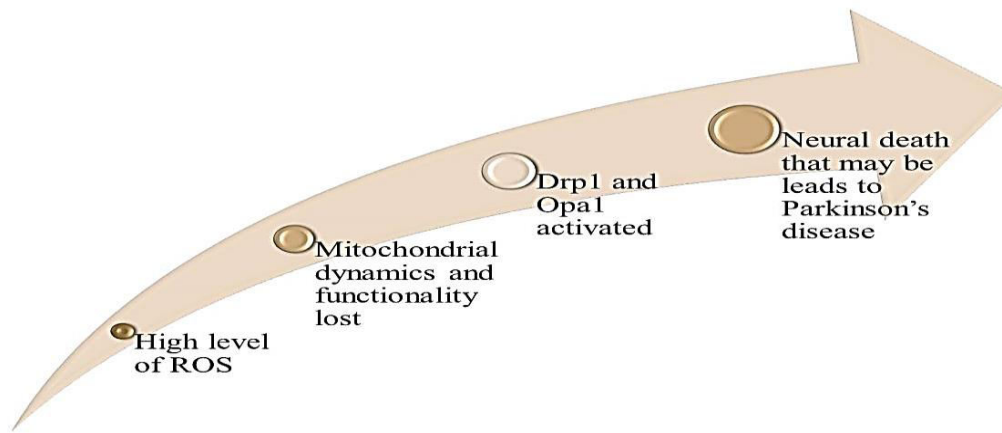


Fig. 2: Schematics cause of PD.

dynamics and ROS warranted, therapeutic target for the treatment of neurodegenerative disease including Parkinson's disease. In this review the cause of PD with recent data is discussed and then suggested a new research approach that could be helpful.

Mitochondrial Dynamics:

Mitochondria are always dividing and fusing to control numbers, their size, and morphology. They exist both individual and interlocked networks. The constant cristae remodelling, the fission and fusion of the mitochondrial membranes helps itself to achieve its morphology. All in all, these methods are known as mitochondrial dynamics (Pernas and Scorrano, 2016). Mitochondrial dynamics depend on onproteolytic and posttranslational modifications of the core proteins involved in the process (Cho *et al.*, 2012). The control of the number and supply of mitochondria, as well as in the response to deviations in energetic cellular requirements, the disposal of damaged mitochondria and maintaining of the components of the respiratory chain, the cristae shape and the ATP production in all Mitochondrial fission chip is very important finding. To sustain cell homeostasis, fusion play pronounced role that take in the junction of outer and inner mitochondrial membrane as an alteration to assist message between Mitochondria and host both (Pernas and Scorrano, 2016). Fusion is also important which is linked to the maintenance of the capability of the mitochondria

to conserve biochemical similarity, and genetic, agree to the degeneracy of ROS, the conversation of mutated DNA, and the repolarization of membranes to retain mitochondrial functionality. The structural and functional prestige of mitochondria is synchronized by Fission and fusion (Santel and Frank, 2008).

Combination and Breaking up Process of Mitochondria:

Mitochondrial dynamics is vastly synchronized by at least four well-maintained dynamin-related GTPases that facilitate the membrane transformation over and done with the junction of mitochondrial membrane (Westermann, 2010). Dynamin-related protein 1 (Drp1), which controls mitochondrial division, on the other mitofusins 1 and 2 (Mfn1 and Mfn2) and optic atrophy 1 (Opa1), which drive fusion. Dynamin-Related Protein (DRP1, in humans), which switches splitting up of the mitochondrial outer membrane (Ingberman *et al.*, 2005; Karbowski *et al.*, 2007; Chang and Blackstone, 2007; Mears *et al.*, 2011). Their part in separation is well-maintained in all the characterized eukaryotes. Numerous proteins play the role of the Peace Corps shifting the outer and inner membranes along the fusion pathway. These proteins include Mitofusins, Fzo (Fuzzy onions) in flies and yeast, as well as human Mfn1, Mfn2 GTPases and Opa1 (Karren *et al.*, 2005). It is found that Mfn1 and Mfn2 share N-terminal sections, where the GTPase territories in charge for the binding and hydrolysis of GTP (Huang *et al.*

al., 2011; Palmer *et al.*, 2011) (Fig. 3, Table 1). Mitofusins are phosphorylation for the regulation of the mitochondrial fusion and ubiquitination to assist mitophagy, i.e., the mitochondria elimination by autophagy (Leboucher *et al.*, 2012). Opa1 is found at the inner mitochondrial membrane and amalgamated in the cytoplasm. It is processed in the mitochondrial matrix. The profile and the distance of the mitochondrial cristae regulated Opa1, for the duration of apoptosis through the involvement of L-Opa and S-Opa (Frezza *et al.*, 2006). Mitochondria is the energy stock and perform so many different physical routes-- cell division, metabolism apoptosis, and bioenergetics also (Chen *et al.*, 2003; Westermann, 2010; Otera and Mihara, 2011; Gomes *et al.*, 2011). Recent studies suggest mitochondrial dynamics processes when got changed that could be cause of human illnesses (Cho *et al.*, 2010). On the other, the human heritable diseases are also linked to defect in fusion and fission proteins, like Drp1 in a development, microcephaly, in syndromes such as sudden death, and inattentiveness to soreness (Waterham *et al.*, 2007). Not only that but also mitochondrial dynamics proteins like mitofusins, is allied with pulmonary hypertension, breast cancer and diabetes mellitus (Zhao *et al.*, 2013). On the other, Opa1 relates with hypertension also.

Morphological Changes in Mitochondria:

Neurons is a well-timed and fitting transport and circulation of mitochondria needed for the energy and calcium which is important for the regulation for the neuronal synaptic broadcast along with the process called vesicle salvaging (Sheng and Cai, 2012). The primary source of energy in neuron is oxidative phosphorylation, which is vigorous to regulate commotion of pumps and transporters, fission and fusion that involve large ATP (Table 1; Fig. 3) (Kuznetsov and Margreiter, 2009). In neurons it is important to carry mitochondria to places where high amount of energy is essential, like synaptic terminals (Otera and Mihara, 2011). The failure of neurons to keep the ATP production mandatory for neuronal electrical activity and

axonal transport is necessary for neuronal communication and calcium regulation (Wakabayashi *et al.*, 2009).

Mitochondria in Disease:

In neurodegenerative diseases diverse neuronal inhabitants are affected. In all circumstances a common complaint is an unusual mitochondrial structure and function that tell us about the facilitation or extension of mitochondrial dysfunction and neuronal death during the course of neurodegenerative disorders (Jellinger, 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). 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). Dereglulation 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. 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). 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), suggesting a close correlation between α -synuclein and 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). Parkin recognizes proteins of the mitochondria in response to cellular insults

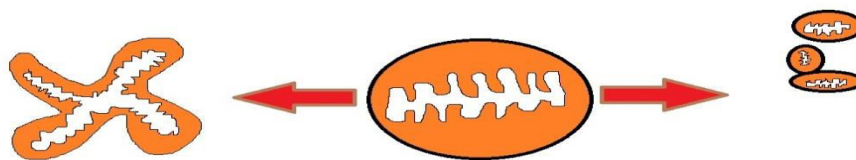


Fig. 3: Mitochondria fission and fusion.

Table1: Key proteins involved in the fission and fusion of mitochondria and their expression (Filichia *et al.*, 2016; Gautier *et al.*, 2016; Ordonez *et al.*, 2017; Carolina Cadastre *et al.*, 2018)

Protein	Disease	Function	Expression
Drp1	PD	Fission	High
Opa1	PD	Fission	High
Mnf2	PD	Fusion	Low

and promotes the repair of mitochondria through 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. 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, 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. 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 (Table 1).

Effect of Calcium and ROS on Mitochondrial Dynamics:

Calcium the cellular courier is involved in signalling pathways that regulate numerous processes. In the nervous system, calcium is critical for several events, including synaptic transmission and cell migration etc. 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. Drp1 in neurons is regulated by calcium through the participation of calcineurin. In addition, under excitotoxic conditions, the levels

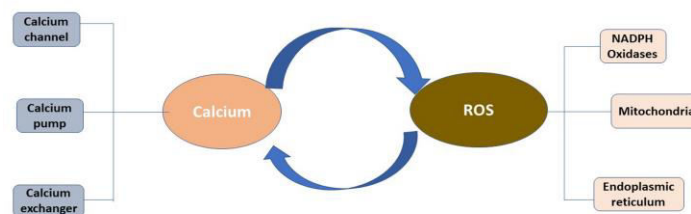


Fig. 4: Calcium and ROS in mutual interplay on mitochondrial dynamics.

of Drp1 and Opa1 are mainly affected by a rise in intracellular calcium (Wang *et al.*, 2015).

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. ROS are reactive metabolites of oxygen that can be radicals, such as superoxide anion and hydroxyl anion, or no-radicals, including hydrogen peroxide. The redox signalling is important for the mitochondrial dynamics in several cell types and 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. 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. That ROS production is involved in this process, and showing that mitochondrial fission capacity is important to avoid neurodegeneration (Kageyama *et al.*, 2012) viability. 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) (Fig. 4).

Conclusion

Increasing evidence suggests that the alteration of mitochondrial dynamics is important in several neurodegenerative diseases like Parkinson's disease. The cellular ROS levels stimulus the expression and activity of Drp1, Opa1, and mitofusins, which in turn control the neuronal fortune. For several neurodegenerative disorders the role of ROS in the regulation of mitochondrial dynamics is critical. Imbalance of ROS is the earliest signals in the pathophysiological process of neurodegeneration. So to investigate the impermanent course of ROS changes in next of kin to the proteins involved in fission or fission, as well as in the molecular pathways that are activated in this route. Thus, strategies to modify both the ROS construction and unusual mitochondrial dynamics and its function may be an smart therapeutic target for the management of neurodegenerative diseases which may be in case of Parkinson's disease also. Further studies are needed in this field.

Acknowledgements

This study was supported by Principal and Faculty members of Microbiology Department,

Ramakrishna Mission Vidyamandira, Belur Math, Howrah, India.

References

- Burte F, Carelli V, Chinnery PF and Yu-Wai-Man P. (2015) Disturbed mitochondrial dynamics and neurodegenerative disorders. *Nat Rev Neurol*. 11(1): 11-24.
- Bertholet AM, Delerue T, Millet AM, Moulis MF, David C, Daloyau M, Arnauné-Pelloquin L, Davezac N, Mils V, Miquel MC, Rojo M and Belenguer P. (2016) Mitochondrial fusion/fission dynamics in neurodegeneration and neuronal plasticity. *Neurobiol Dis*. 90: 3-19.
- Carolina CC, Hernández-Espinosa DR and Morán J. (2018) ROS as regulators of mitochondrial dynamics in neurons. *Cell Mol Neurobiol*. 38(5): 995-1007.
- Chang CR and Blackstone C. (2007) Drp1 phosphorylation and mitochondrial regulation. *EMBO J*. 26(24): 6488-6497.
- Chen H, Detmer SA, Ewald AJ, Griffin EE, Fraser SE and Chan DC. (2003) Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. *J Cell Biol*. 160: 189-200.
- Cho MH, Kim DH, Choi JE, Chang EJ and Seung Y. (2012) Increased phosphorylation of dynamin-related protein 1 and mitochondrial fission in okadaic acid-treated neurons. *Brain Res*. 1454: 100-110.
- Cho SG. (2010) Drp1 dephosphorylation in ATP depletion-induced mitochondrial injury and tubular cell apoptosis. *Am J Physiol Renal Physiol*. 299(1): F199-F206.
- Devoto MP, Dimopoulos N, Alloatti M, Pardi MB, Saez TM, Otero MG and Falzone TL. (2017) α synuclein control of mitochondrial homeostasis in human-derived neurons is disrupted by mutations associated with Parkinson's disease. *Sci Rep*. 7(1):1-13.
- Elena Ingerman Perkins EM, Marino M, Mears JA, McCaffery JM, Hinshaw JE and Nunnari J. (2005) Dnm1 forms spirals that are structurally tailored to fit mitochondria. *J Cell Biol*. 170(7): 1021-1027.
- Fischer TD, Hylin MJ, Zhao J, Moore AN, Waxham MN and Dash PK. (2016) Altered mitochondrial dynamics and TBI pathophysiology. *Front Syst Neurosci*. 10: 29.
- Flippo KH and Strack S. (2017) An emerging role for mitochondrial dynamics in schizophrenia. *Schizophr Res*. 187: 26-32.
- Frezza C. (2017) Mitochondrial metabolites: undercover signalling molecules. *Interface Focus*. 7(2): 20160100.
- Frezza C, Cipolat S, Martins de Brito O, Micaroni M, Beznoussenko GV, Rudka T, Bartoli D, Polishuck RS, Danial NN, De Strooper B and Scorrano L. (2006) OPA1 controls apoptotic cristae remodeling independently from mitochondrial fusion. *Cell*. 126(1): 177-189.
- Gao J, Wang L, Liu J, Xie F, Su B and Wang X. (2017) Abnormalities of mitochondrial dynamics in neurodegenerative diseases. *Antioxidants*. 6(2): 25.
- Gautier CA, Erpapazoglou Z, Mouton-Liger F, Muriel MP, Cormier F, Bigou S, Duffaure S, Girard M, Foret B, Iannielli A, Broccoli V, Dalle C, Bohl D, Michel PP, Corvol JC, Brice A and Corti O. (2016) The endoplasmic reticulum-mitochondria interface is perturbed in PARK2 knockout mice and patients with PARK2 mutations. *Hum Mol Genet*. 25(14): 2972-2984.
- Goldman JG and Postuma R. (2014) Premotor and nonmotor features of Parkinson's disease. *Curr Opin Neurol*. 27(4): 434-441.
- Gomes LC, Di Benedetto G and Scorrano L. (2011) During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. *Nat Cell Biol*. 13: 589-598.
- Gray JJ, Zommer AE, Bouchard RJ, Duval N, Blackstone C and Linseman DA. (2013) N-terminal cleavage of the mitochondrial fusion GTPase OPA1 occurs via a caspase-independent mechanism in cerebellar granule neurons exposed to oxidative or nitrosative stress. *Brain Res*. 1494: 28-43.
- Huang P, Galloway CA and Yoon Y. (2011) Control of mitochondrial morphology through differential interactions of mitochondrial fusion and fission proteins. *PLoS One*. 6(5): e20655.
- James SJ, Schumacker PT, Guzman JD, Ilijic E, Yang B and Zampese E. (2017) Calcium and Parkinson's disease. *Biochem Biophys Res Commun*. 483(4): 1013-1019.
- Jellinger KA. (2009) Recent advances in our understanding of neurodegeneration. *J Neural Transm*. 116(9): 1111-1162.
- Kageyama Y, Zhang Z, Roda R, Fukaya M, Wakabayashi J, Wakabayashi N and Sesaki H. (2012) Mitochondrial division ensures the survival of postmitotic neurons by suppressing oxidative damage. *J Cell Biol*. 197(4): 535-551.
- Karbowsky M, Neutzner A and Youle RJ. (2007) The mitochondrial E3 ubiquitin ligase MARCH5 is required for Drp1 dependent mitochondrial division. *J Cell Biol*. 178(1): 71-84.
- Karren MA, Coonrod EM, Anderson TK and Shaw JM.

- (2005) The role of Fis1p-Mdv1p interactions in mitochondrial fission complex assembly. *J Cell Biol* 171(2): 291-301.
- Knott AB, Perkins G, Schwarzenbacher R and Bossy-Wetzel E. (2008) Mitochondrial fragmentation in neurodegeneration. *Nat Rev Neurosci* 9(7): 505-518.
- Kuznetsov AV and Margreiter R. (2009) Heterogeneity of mitochondria and mitochondrial function within cells as another level of mitochondrial complexity. *Int J Mol Sci* 10(4):1911-1929.
- Lackner LL. (2014) Shaping the dynamic mitochondrial network. *BMC Biol* 12(1): 35.
- Leboucher G.P. (2012) Stress-induced phosphorylation and proteasomal degradation of mitofusin 2 facilitates mitochondrial fragmentation and apoptosis. *Mol Cell* 47(4): 547-557.
- Mears JA, Lackner LL, Fang S, Ingberman E, Nunnari J and Hinshaw JE. (2011) Conformational changes in Dnm1 support a contractile mechanism for mitochondrial fission. *Nat Struct Mol Biol* 18(1): 20-26.
- Onyou Hwang. (2013) Role of oxidative stress in Parkinson's disease. *Exp Neurobiol* 22(1): 11-17.
- Ordonez DG, Lee MK and Feany MB. (2017) α -synuclein induces mitochondrial dysfunction through spectrin and the actin cytoskeleton. *Neuron* 97(1):108-124.
- Otera H and Mihara K. (2014) Discovery of the membrane receptor for mitochondrial fission GTPase Drp1. *Small GTPases* 2(3):167-172
- Palmer CS, Osellame LD, Laine D, Koutsopoulos OS, Frazier AE and Ryan MT. (2011) MiD49 and MiD51, new components of the mitochondrial fission machinery. *EMBO Rep* 12(6): 565-573.
- Pernas L and Scorrano L. (2016) Mito-Morphosis: Mitochondrial fusion, fission, and cristae remodeling as key mediators of cellular function. *Annu Rev Physiol* 78: 505-531.
- Pringsheim T, Jette N, Frolkis A and Steeves TD. (2014) The prevalence Parkinson's disease: a systematic review and metaanalysis. *Mov Disord* 29(13): 1583-1590.
- Rietdijk CD, Perez-Pardo P, Garssen J, van Wezel RJ and Kraneveld AD. (2014) Exploring Braak's hypothesis of Parkinson's disease. *Front Neurol* 8: 37.
- Ryan J, Dasgupta A, Huston J, Chen KH and Archer SL. (2015) Mitochondrial dynamics in pulmonary arterial hypertension. *J Mol Med (Berl)* 93(3): 229-242.
- Santel A and Frank S. (2008) Shaping mitochondria: The complex posttranslational regulation of the mitochondrial fission protein DRP1. *IUBMB Life* 60(7): 448-455.
- Seirafi M, Kozlov G and Gehring K. (2015) Parkin structure and function. *FEBS J* 282(11): 2076-2088.
- Sheng ZH and Cai Q. (2012) Mitochondrial transport in neurons: impact on synaptic homeostasis and neurodegeneration. *Nat Rev Neurosci* 13(2): 77-93.
- Wakabayashi J, Zhang Z, Wakabayashi N, Tamura Y, Fukaya M, Kensler TW, Iijima M and Sesaki H. (2009) The dynamin-related GTPase Drp1 is required for embryonic and brain development in mice. *J Cell Biol* 186: 805-816.
- Wang DB, Garden GA, Kinoshita C, Wyles C, Babazadeh N, Sopher B, Kinoshita Y and Morrison RS. (2013) Changes in mitochondrial length and neuronal death. *J Neurosci* 33(4):1357-1365.
- Wang L, Duan Q, Wang T, Ahmed M, Zhang N, Li Y, Li L and Yao X. (2015) Mitochondrial respiratory chain inhibitors involved in ros production induced by acute high concentrations of iodide and the effects of SOD as a protective factor. *Oxid Med Cell Longev* 2015: 217670.
- Waterham HR, Koster J, van Roermund CW, Mooyer PA, Wanders RJ and Leonard JV. (2007) A lethal defect of mitochondrial and peroxisomal fission. *N Engl J Med* 356:1736-1741.
- Westermann B. (2010) Mitochondrial fusion and fission in cell life and death. *Nature Rev Molec Cell Biol* 11(12): 872-884.
- Zhao J, Zhang J, Yu M, Xie Y, Huang Y, Wolff DW, Abel PW and Tu Y. (2013) Mitochondrial dynamics regulates migration and invasion of breast cancer cells. *Oncogene* 32(40): 4814-4824.